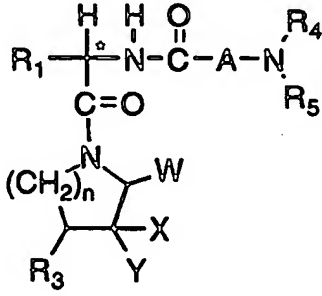




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| <p>(21) International Application Number: PCT/US94/12816</p> <p>(22) International Filing Date: 7 November 1994 (07.11.94)</p> <p>(30) Priority Data:</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%;">149,441</td> <td style="width: 40%;">9 November 1993 (09.11.93)</td> <td style="width: 30%;">US</td> </tr> <tr> <td>165,149</td> <td>10 December 1993 (10.12.93)</td> <td>US</td> </tr> <tr> <td>173,449</td> <td>23 December 1993 (23.12.93)</td> <td>US</td> </tr> <tr> <td>323,994</td> <td>17 October 1994 (17.10.94)</td> <td>US</td> </tr> <tr> <td>323,998</td> <td>17 October 1994 (17.10.94)</td> <td>US</td> </tr> <tr> <td>323,988</td> <td>17 October 1994 (17.10.94)</td> <td>US</td> </tr> </table> <p>(60) Parent Applications or Grants</p> <p>(63) Related by Continuation</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%;">US</td> <td style="width: 40%;">323,994 (CIP)</td> <td style="width: 30%;"></td> </tr> <tr> <td>Filed on</td> <td>17 October 1994 (17.10.94)</td> <td></td> </tr> <tr> <td>US</td> <td>323,998 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>17 October 1994 (17.10.94)</td> <td></td> </tr> <tr> <td>US</td> <td>323,988 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>17 October 1994 (17.10.94)</td> <td></td> </tr> </table> <p>(71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> | | | 149,441 | 9 November 1993 (09.11.93) | US | 165,149 | 10 December 1993 (10.12.93) | US | 173,449 | 23 December 1993 (23.12.93) | US | 323,994 | 17 October 1994 (17.10.94) | US | 323,998 | 17 October 1994 (17.10.94) | US | 323,988 | 17 October 1994 (17.10.94) | US | US | 323,994 (CIP) | | Filed on | 17 October 1994 (17.10.94) | | US | 323,998 (CIP) | | Filed on | 17 October 1994 (17.10.94) | | US | 323,988 (CIP) | | Filed on | 17 October 1994 (17.10.94) | | <p>(72) Inventors; and (75) Inventors/Applicants (for US only): MORRIELLO, Gregori, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). PATCHETT, Arthur, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). YANG, Lihu [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). CHEN, Meng, H. [-/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). NARGUND, Ravi [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> <p>(74) Common Representative: MERCK & CO., INC.; Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> <p>(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).</p> <p>Published With international search report.</p> |
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| <p>(54) Title: PIPERIDINES, PYRROLIDINES AND HEXAHYDRO-1H-AZEPINES PROMOTE RELEASE OF GROWTH HORMONE</p> <p>(57) Abstract</p> <p>The present invention is directed to certain piperidine, pyrrolidine, and hexahydro-1H-azepine compounds of general structural formula (I) wherein R₁, R₃, R₄, R₅, A, W, X, Y, and n are as defined herein. These compounds promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to treat physiological or medical conditions characterized by a deficiency in growth hormone secretion, such as short stature in growth hormone deficient children, and to treat medical conditions which are improved by the anabolic effects of growth hormone. Growth hormone releasing compositions containing such compounds as the active ingredient thereof are also disclosed.</p> | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|  <p style="text-align: right;">(I)</p> | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

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TITLE OF THE INVENTION

PIPERIDINES, PYRROLIDINES AND HEXAHYDRO-1H-AZEPINES PROMOTE RELEASE OF GROWTH HORMONE

5 CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of copending application Serial No. 08/323,994, filed October 17, 1994, which is a continuation-in-part of copending application Serial No. 08/149,441, filed November 9, 1993; a continuation-in-part of copending
10 application Serial No. 08/323,998, filed October 17, 1994, which is a continuation-in-part of copending application Serial No. 08/165,149, filed December 10, 1993; and a continuation-in-part of copending application Serial No. 08/323,988, filed October 17, 1994, which is a continuation-in-part of copending application Serial No. 08/173,449,
15 filed December 23, 1993.

BACKGROUND OF THE INVENTION

Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing.
20 In addition, growth hormone is known to have the following basic effects on the metabolic processes of the body: (1) Increased rate of protein synthesis in all cells of the body; (2) Decreased rate of carbohydrate utilization in cells of the body; (3) Increased mobilization of free fatty acids and use of fatty acids for energy. A deficiency in growth hormone
25 secretion can result in various medical disorders, such as dwarfism.

Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth
30 hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

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In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering GRF or a peptidal compound which stimulated growth hormone production and/or release. In either
5 case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted
10 to the recipient of the growth hormone. Recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray.

Other compounds have been developed which stimulate
15 the release of endogenous growth hormone such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent 4,411,890. These peptides, while considerably smaller than growth hormones are still susceptible to various proteases. As with most peptides, their potential for oral bioavailability is low. Non peptidal growth hormone
20 secretagogues with a benzolactam structure are disclosed in U.S. Patents 5,206,235, 5,283,241, 5,284,841, 5,310,737 and 5,317,017. The instant compounds are low molecular weight peptide analogs for promoting the release of growth hormone which have good stability in a variety of physiological environments and which may be
25 administered parenterally, nasally or by the oral route.

SUMMARY OF THE INVENTION

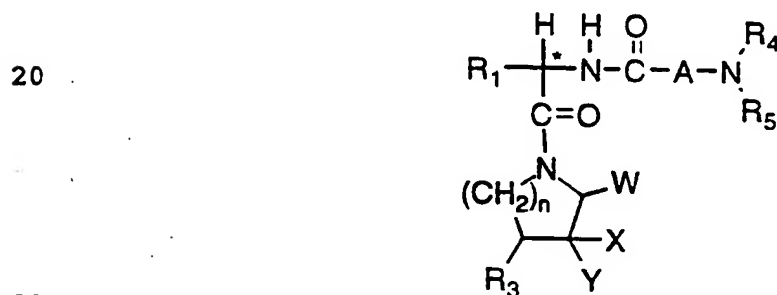
The instant invention is directed to certain piperidine, pyrrolidine, and hexahydro-1H-azepine compounds which have the
30 ability to stimulate the release of natural or endogenous growth hormone. The compounds thus have the ability to be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food production where the

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stimulation of growth hormone will result in a larger, more productive animal. Thus, it is an object of the instant invention to describe the piperidine, pyrrolidine, and hexahydro-1H-azepine compounds. It is a further object of this invention to describe procedures for the preparation of such compounds. A still further object is to describe the use of such compounds to increase the secretion of growth hormone in humans and animals. A still further object of this invention is to describe compositions containing the piperidine, pyrrolidine, and hexahydro-1H-azepine compounds for the use of treating humans and animals so as to increase the level of growth hormone secretions. Further objects will become apparent from a reading of the following description.

DESCRIPTION OF THE INVENTION

The novel piperidine, pyrrolidine, and hexahydro-1H-azepine compounds of the instant invention are best described in the following structural formula I:



Formula I

wherein:

R₁ is selected from the group consisting of:
 C₁-C₁₀ alkyl, aryl, aryl(C₁-C₆ alkyl), (C₃-C₇ cycloalkyl)(C₁-C₆ alkyl)-, (C₁-C₅ alkyl)-K-(C₁-C₅ alkyl)-, aryl(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, and (C₃-C₇ cycloalkyl)(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, where K is O, S(O)_m, N(R₂)C(O), C(O)N(R₂), OC(O), C(O)O, -CR₂=CR₂-, or -C≡C-, where aryl is selected from: phenyl, naphthyl, indolyl, azaindole, pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl. and R₂ and alkyl may be further substituted by 1 to 9 halogen, S(O)_mR_{2a}. 1

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to 3 of OR_{2a} or C(O)OR_{2a}, and aryl may be further substituted by 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of OR₂, methylenedioxy, -S(O)_mR₂, 1 to 2 of -CF₃, -OCF₃, nitro, -N(R₂)C(O)(R₂), -C(O)OR₂, -C(O)N(R₂)(R₂), -1H-tetrazol-5-yl, -SO₂N(R₂)(R₂), -N(R₂)SO₂ phenyl, or -N(R₂)SO₂R₂;

R₂ is selected from: hydrogen, C₁-C₆ alkyl, and C₃-C₇ cycloalkyl, and where two C₁-C₆ alkyl groups are present on one atom, they may be optionally joined to form a C₃-C₈ cyclic ring, optionally including oxygen, sulfur or NR_{3a};

R_{2a} is hydrogen, or C₁-C₆ alkyl optionally substituted by hydroxyl;

R₃ is selected from: hydrogen, -(CH₂)_rphenyl, -(CH₂)_rnaphthyl, -C₁-C₁₀ alkyl, -C₃-C₇ cycloalkyl, where the phenyl, naphthyl and C₃-C₇ cycloalkyl rings may be substituted by 1 to 3 substituents selected from the group consisting of: C₁-C₆ alkyl, halogen, -OR₂, -NHSO₂CF₃, -(CH₂)_rOR₆, -(CH₂)_rN(R₂)(R₆), -(CH₂)_r(R₆), -(CH₂)_rC(O)OR₂, -(CH₂)_rC(O)OR₆, -(CH₂)_rOC(O)R₂, -(CH₂)_rOC(O)R₆, -(CH₂)_rC(O)R₂, -(CH₂)_rC(O)R₆, -(CH₂)_rC(O)N(R₂)(R₂), -(CH₂)_rC(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)R₂, -(CH₂)_rN(R₂)C(O)R₆, -(CH₂)_rN(R₆)C(O)R₂, -(CH₂)_rN(R₆)C(O)R₆, -(CH₂)_rN(R₂)C(O)OR₂, -(CH₂)_rN(R₂)C(O)OR₆, -(CH₂)_rN(R₆)C(O)OR₂, -(CH₂)_rN(R₆)C(O)OR₆, -(CH₂)_rN(R₂)C(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)N(R₂)(R₂), -(CH₂)_rN(R₆)C(O)N(R₂)(R₆), (CH₂)_rN(R₂)SO₂R₆, -(CH₂)_rN(R₂)SO₂R₂, -(CH₂)_rN(R₆)SO₂R₂, (CH₂)_rN(R₆)SO₂R₆, -(CH₂)_rOC(O)N(R₂)(R₆), -(CH₂)_rOC(O)N(R₂)(R₂), -(CH₂)_rSO₂N(R₂)(R₆), -(CH₂)_rSO₂N(R₂)(R₂), (CH₂)_rSO₂NHC(O)R₆, -(CH₂)_rSO₂NHC(O)R₂, -(CH₂)_rSO₂NHC(O)OR₆, -(CH₂)_rSO₂NHC(O)OR₂, -(CH₂)_rC(O)NHC(O)NR₂, -(CH₂)_rC(O)NHC(O)NR₆, -(CH₂)_rC(O)NHC(O)R₂, -(CH₂)_rCONHC(O)R₆, -(CH₂)_rCONHSO₂R₆, -(CH₂)_rCONHSO₂R₂, -(CH₂)_rCONHSO₂N(R₂)R₂, -(CH₂)_rCONHSO₂N(R₂)R₆,

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-(CH₂)_rN(R₂)SO₂N(R₂)R₆), -(CH₂)_rN(R₆)SO₂N(R₂)R₆),
 -(CH₂)_rS(O)_mR₆, and -(CH₂)_rS(O)_mR₂;

R_{3a} is hydrogen, or C₁-C₆ alkyl optionally substituted by hydroxyl;

5

W is selected from the group consisting of: hydrogen,
 -CN, -C(O)OR₈, -C(O)OR₂, -C(O)O(CH₂)_laryl, -C(O)N(R₂)(R₂);
 -C(O)N(R₂)(R₈), -C(O)N(R₂)(CH₂)_laryl, -CH₂N(R₂)C(O)R₈
 -CH₂N(R₂)C(O)(CH₂)_laryl, -(CH₂)_rOR₂, -CH(OH)R₂,
 10 -CH(OH)(CH₂)_laryl, -C(O)R₂, -C(O)(CH₂)_laryl, 1H-tetrazol-5-yl,
 5-amino-1, 2, 4-oxadiazol-3-yl, and 5-methyl-1, 2, 4-oxadiazol-3-yl,
 where R₈ is hydrogen, C₁-C₆ alkyl, or C₁-C₆ alkyl substituted by
 OR₂, C(O)OR₂, CON(R₂)(R₂), N(R₂)C(O)R₂,
 N(R₂)C(O)N(R₂)(R₂), and aryl is phenyl, pyridyl, or 1H-tetrazol-5-
 15 yl;

X is selected from the group consisting of: hydrogen, -C≡N,
 -(CH₂)_qN(R₂)C(O)R₂, -(CH₂)_qN(R₂)C(O)(CH₂)_taryl,
 -(CH₂)_qN(R₂)SO₂(CH₂)_taryl, -(CH₂)_qN(R₂)SO₂R₂,
 20 -(CH₂)_qN(R₂)C(O)N(R₂)(CH₂)_taryl, -(CH₂)_qN(R₂)C(O)N(R₂)(R₂),
 -(CH₂)_qC(O)N(R₂)(R₂), -(CH₂)_qC(O)N(R₂)(CH₂)_taryl,
 -(CH₂)_qC(O)OR₂, -(CH₂)_qC(O)O(CH₂)_taryl, -(CH₂)_qOR₂,
 -(CH₂)_qOC(O)R₂, -(CH₂)_qOC(O)(CH₂)_taryl,
 -(CH₂)_qOC(O)N(R₂)(CH₂)_taryl, -(CH₂)_qOC(O)N(R₂)(R₂),
 25 -(CH₂)_qC(O)R₂, -(CH₂)_qC(O)(CH₂)_taryl,
 -(CH₂)_qN(R₂)C(O)OR₂, -(CH₂)_qN(R₂)SO₂N(R₂)(R₂),
 -(CH₂)_qS(O)_mR₂, and -(CH₂)_qS(O)_m(CH₂)_taryl, where an R₂, (CH₂)_q
 and (CH₂)_t group may be optionally substituted by 1 to 2 C₁-C₄ alkyl,
 hydroxyl, C₁-C₄ lower alkoxy, carboxyl, CONH₂, S(O)_mCH₃,
 30 carboxylate C₁-C₄ alkyl esters, or 1H-tetrazol-5-yl. and aryl is phenyl,
 naphthyl, pyridyl, thiazolyl, or 1H-tetrazol-5-yl groups which may be
 optionally substituted by 1 to 3 halogen, 1 to 3 -OR₂, -CON(R₂)(R₂),
 -C(O)OR₂, 1 to 3 C₁-C₄ alkyl, -S(O)_mR₂, or 1H-tetrazol-5-yl;

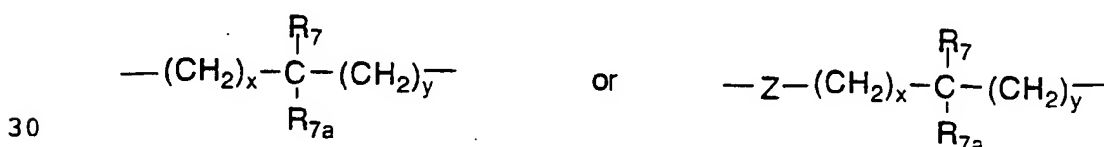
- 6 -

Y is selected from the group consisting of:
 hydrogen, C₁-C₁₀ alkyl, -(CH₂)_taryl,
 -(CH₂)_q(C₃-C₇ cycloalkyl), -(CH₂)_q-K-(C₁-C₆ alkyl),
 -(CH₂)_q-K-(CH₂)_taryl, -(CH₂)_q-K-(CH₂)_t(C₃-C₇ cycloalkyl)
 5 containing O, NR₂, S), and -(CH₂)_q-K-(CH₂)_t(C₃-C₇ cycloalkyl), where
 K is O, S(O)_m, C(O)NR₂, CH=CH, C≡C, N(R₂)C(O), C(O)NR₂, C(O)O,
 or OC(O), and where the alkyl, R₂, (CH₂)_q and (CH₂)_t groups may be
 optionally substituted by C₁-C₄ alkyl, hydroxyl, C₁-C₄ lower alkoxy,
 carboxyl, -CONH₂ or carboxylate C₁-C₄ alkyl esters, and aryl is phenyl,
 10 naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl,
 pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiophenyl,
 quinolinyl, pyrraziny, or isothiazolyl which is optionally substituted by 1
 to 3 halogen, 1 to 3 -OR₂, -C(O)OR₂, -C(O)N(R₂)(R₂), nitro, cyano,
 benzyl, 1 to 3 C₁-C₄ alkyl, -S(O)_mR₂, or 1H-tetrazol-5-yl;
 15 with the proviso that at least one of R₃, W, X, and Y are other than
 hydrogen;

R₄ and R₅ are independently hydrogen, C₁-C₆ alkyl, substituted C₁-
 C₆ alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxy, 1
 20 to 3 C₁-C₁₀ alkanoyloxy, 1 to 3 C₁-C₆ alkoxy, phenyl, phenoxy, 2-
 furyl, C₁-C₆ alkoxy carbonyl, S(O)_m(C₁-C₆ alkyl); or R₄ and R₅ can
 be taken together to form -(CH₂)_dL_a(CH₂)_e- where L_a is C(R₂)₂, O,
 S(O)_m or N(R₂), d and e are independently 1 to 3 and R₂ is as defined
 above;

25

A is:



where x and y are independently 0, 1, 2 or 3;

Z is N-R_{6a} or O, where R_{6a} is hydrogen or C₁-C₆ alkyl;

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- R₆ is hydrogen, C₁-C₆ alkyl, or (CH₂)_varyl, wherein the alkyl and (CH₂)_v groups may be optionally substituted by 1-2 O(R₂), S(O)_mR₂, 1H-tetrazol-5-yl, C(O)OR₂, C(O)N(R₂)(R₂) or SO₂N(R₂)(R₂),
5 N(R₂)C(O)N(R₂)(R₂), and wherein aryl is phenyl, pyridyl, 1H-tetrazol-5-yl, triazolyl, imidazolyl, thiazolyl, pyrazolyl, thiadiazolyl, imidazolone-1-yl, benzimidazol-2-yl, triazolinone-yl optionally substituted with C₁-C₆ alkyl, C₃-C₆ cycloalkyl, amino, or hydroxyl;
- 10 R₇ and R_{7a} are independently hydrogen, C₁-C₆ alkyl, trifluoromethyl, phenyl, substituted C₁-C₆ alkyl where the substituents are imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)_mR₂, C(O)O(C₁-C₆ alkyl), C₃-C₇ cycloalkyl, N(R₂)(R₂), C(O)N(R₂)(R₂); or R₇ and R_{7a} can
15 independently be joined to one or both of R₄ and R₅ groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R₇ or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms; or R₇ and R_{7a} can be joined to one another to form a C₃-C₇ cycloalkyl;
- l is 0, 1 or 2;
20 m is 0, 1, or 2;
n is 1, 2, or 3;
q is 0, 1, 2, 3, or 4;
r is 0, 1, 2, or 3;
t is 0, 1, 2, or 3;
v is 0, 1, or 2 ;

25 and pharmaceutically acceptable salts and individual diastereomers thereof.

When n is 1, a pyrrolidine ring is formed, when n is 2 a piperidine ring is formed and when n is 3 the ring is designated as a
30 hexahydro-1H-azepine.

In the above structural formula and throughout the instant specification, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration which may optionally contain double or triple

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bonds. Exemplary of such alkyl groups are methyl (Me), ethyl (Et), propyl (Pr), isopropyl (i-Pr), butyl (Bu), sec-butyl (s-Bu), tertiary butyl (t-Bu), pentyl, isopentyl, hexyl, isohexyl, allyl, propinyl, butadienyl, hexenyl and the like.

5 The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary
10 butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy, allyloxy, propinyloxy, isobutenyloxy, hexenyloxy and the like.

 The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

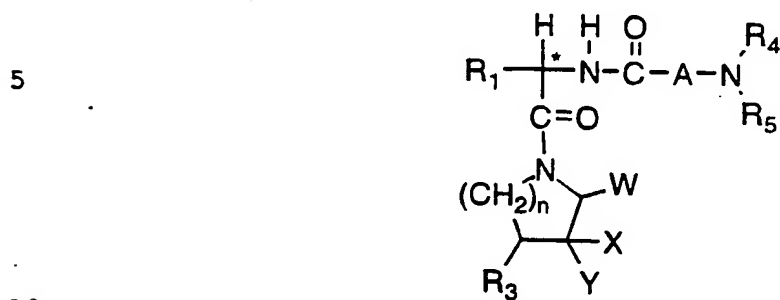
 The term "aryl" within the present invention, unless
15 otherwise specified, is intended to include aromatic rings, such as carbocyclic and heterocyclic aromatic rings selected the group consisting of: phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiopheneyl, quinolinyl, pyrraziny, or isothiazolyl, which may be
20 optionally substituted by 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of -OR², methylenedioxy, -S(O)_mR², 1 to 2 of -CF₃, -OCF₃, nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)(R²), -1H-tetrazol-5-yl, -SO₂N(R²)(R²), -N(R²)SO₂ phenyl, or -N(R²)SO₂R², wherein R² is as
25 defined herein.

 Certain of the above defined terms may occur more than once in the above formula or definitions and upon such occurrence, each term shall be defined independently of the other.

30

- 9 -

A first embodiment of the present invention is directed to the compounds of the structural formula AI:



Formula AI

wherein:

R₁ is selected from the group consisting of:
 C₁-C₁₀ alkyl, aryl, aryl(C₁-C₆ alkyl), (C₃-C₇ cycloalkyl)(C₁-C₆ alkyl)-,
 15 (C₁-C₅ alkyl)-K-(C₁-C₅ alkyl)-, aryl(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-,
 and (C₃-C₇ cycloalkyl)(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, where K is O,
 S(O)_m, N(R₂)C(O), C(O)N(R₂), OC(O), C(O)O, -CR₂=CR₂-, or -C≡C-,
 where aryl is selected from: phenyl, naphthyl, indolyl, azaindole,
 pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl, and
 20 R₂ and alkyl may be further substituted by 1 to 9 halogen, S(O)_mR_{2a}, 1
 to 3 of OR_{2a} or C(O)OR_{2a}, and aryl may be further substituted by 1 to 3
 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of OR₂, methylenedioxy,
 -S(O)_mR₂, 1 to 2 of -CF₃, -OCF₃, nitro, -N(R₂)C(O)(R₂), -C(O)OR₂,
 -C(O)N(R₂)(R₂), -1H-tetrazol-5-yl, -SO₂N(R₂)(R₂), -N(R₂)SO₂ phenyl,
 25 or -N(R₂)SO₂R₂;

R₂ is selected from: hydrogen, C₁-C₆ alkyl, and C₃-C₇ cycloalkyl, and
 where two C₁-C₆ alkyl groups are present on one atom, they may be
 optionally joined to form a C₃-C₈ cyclic ring, optionally including
 30 oxygen, sulfur or NR_{3a};

R_{2a} is hydrogen, or C₁-C₆ alkyl optionally substituted by hydroxyl;

R₃ is selected from: hydrogen, -(CH₂)_rphenyl, -(CH₂)_rnaphthyl, -C₁-C₁₀
 alkyl, -C₃-C₇ cycloalkyl, where the phenyl, naphthyl and C₃-C₇
 cycloalkyl rings may be substituted by 1 to 3 substituents selected from

- 10 -

the group consisting of: C₁-C₆ alkyl, halogen, -OR₂, -NHSO₂CF₃,
 -(CH₂)_rOR₆, -(CH₂)_rN(R₂)(R₆), -(CH₂)_r(R₆), -(CH₂)_rC(O)OR₂,
 -(CH₂)_rC(O)OR₆, -(CH₂)_rOC(O)R₂, -(CH₂)_rOC(O)R₆,
 -(CH₂)_rC(O)R₂, -(CH₂)_rC(O)R₆, -(CH₂)_rC(O)N(R₂)(R₂),
 5 -(CH₂)_rC(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)R₂, -(CH₂)_rN(R₂)C(O)R₆,
 -(CH₂)_rN(R₆)C(O)R₂, -(CH₂)_rN(R₆)C(O)R₆, -(CH₂)_rN(R₂)C(O)OR₂,
 -(CH₂)_rN(R₂)C(O)OR₆, -(CH₂)_rN(R₆)C(O)OR₂,
 -(CH₂)_rN(R₆)C(O)OR₆, -(CH₂)_rN(R₂)C(O)N(R₂)(R₆),
 -(CH₂)_rN(R₂)C(O)N(R₂)(R₂), -(CH₂)_rN(R₆)C(O)N(R₂)(R₆),
 10 (CH₂)_rN(R₂)SO₂R₆, -(CH₂)_rN(R₂)SO₂R₂, -(CH₂)_rN(R₆)SO₂R₂,
 (CH₂)_rN(R₆)SO₂R₆, -(CH₂)_rOC(O)N(R₂)(R₆),
 -(CH₂)_rOC(O)N(R₂)(R₂), -(CH₂)_rSO₂N(R₂)(R₆),
 -(CH₂)_rSO₂N(R₂)(R₂), (CH₂)_rSO₂NHC(O)R₆, -(CH₂)_rSO₂NHC(O)R₂,
 -(CH₂)_rSO₂NHC(O)OR₆, -(CH₂)_rSO₂NHC(O)OR₂,
 15 -(CH₂)_rC(O)NHC(O)NR₂, -(CH₂)_rC(O)NHC(O)NR₆,
 -(CH₂)_rC(O)NHC(O)R₂, -(CH₂)_rCONHC(O)R₆,
 -(CH₂)_rCONHSO₂R₆, -(CH₂)_rCONHSO₂R₂,
 -(CH₂)_rCONHSO₂N(R₂)R₂, -(CH₂)_rCONHSO₂N(R₂)R₆,
 -(CH₂)_rN(R₂)SO₂N(R₂)R₆, -(CH₂)_rN(R₆)SO₂N(R₂)R₆,
 20 -(CH₂)_rS(O)_mR₆, and -(CH₂)_rS(O)_mR₂;

R_{3a} is hydrogen, or C₁-C₆ alkyl optionally substituted by hydroxyl;

W is selected from the group consisting of:
 25 -CN, -C(O)OR₈, -C(O)OR₂, -C(O)O(CH₂)_laryl, -C(O)N(R₂)(R₂);
 -C(O)N(R₂)(R₈), -C(O)N(R₂)(CH₂)_laryl, -CH₂N(R₂)C(O)R₈
 -CH₂N(R₂)C(O)(CH₂)_laryl, -(CH₂)_rOR₂, -CH(OH)R₂,
 -CH(OH)(CH₂)_laryl, -C(O)R₂, -C(O)(CH₂)_laryl, 1H-tetrazol-5-yl,
 5-amino-1, 2, 4-oxadiazol-3-yl, and 5-methyl-1, 2, 4-oxadiazol-3-yl,
 30 where R₈ is hydrogen, C₁-C₆ alkyl, or C₁-C₆ alkyl substituted by
 OR₂, C(O)OR₂, CON(R₂)(R₂), N(R₂)C(O)R₂,
 N(R₂)C(O)N(R₂)(R₂), and aryl is phenyl, pyridyl, or 1H-tetrazol-5-yl;

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X is selected from: hydrogen, $-C\equiv N$, $-(CH_2)_qN(R_2)C(O)R_2$,
 $-(CH_2)_qN(R_2)C(O)(CH_2)_taryl$, $-(CH_2)_qN(R_2)SO_2(CH_2)_taryl$,
 $-(CH_2)_qN(R_2)SO_2R_2$, $-(CH_2)_qN(R_2)C(O)N(R_2)(CH_2)_taryl$,
 $-(CH_2)_qN(R_2)C(O)N(R_2)(R_2)$, $-(CH_2)_qC(O)N(R_2)(R_2)$,
5 $-(CH_2)_qC(O)N(R_2)(CH_2)_taryl$, $-(CH_2)_qC(O)OR_2$,
 $-(CH_2)_qC(O)O(CH_2)_taryl$, $-(CH_2)_qOR_2$, $-(CH_2)_qOC(O)R_2$,
 $-(CH_2)_qOC(O)(CH_2)_taryl$, $-(CH_2)_qOC(O)N(R_2)(CH_2)_taryl$,
 $-(CH_2)_qOC(O)N(R_2)(R_2)$, $-(CH_2)_qC(O)R_2$, $-(CH_2)_qC(O)(CH_2)_taryl$,
 $-(CH_2)_qN(R_2)C(O)OR_2$, $-(CH_2)_qN(R_2)SO_2N(R_2)(R_2)$,
10 $-(CH_2)_qS(O)_mR_2$, and $-(CH_2)_qS(O)_m(CH_2)_taryl$, where an R_2 , $(CH_2)_q$
and $(CH_2)_t$ group may be optionally substituted by 1 to 2 C_1 - C_4 alkyl,
hydroxyl, C_1 - C_4 lower alkoxy, carboxyl, $CONH_2$, $S(O)_mCH_3$,
carboxylate C_1 - C_4 alkyl esters, or 1H-tetrazol-5-yl, and aryl is phenyl,
naphthyl, pyridyl, thiazolyl, or 1H-tetrazol-5-yl groups which may be
15 optionally substituted by 1 to 3 halogen, 1 to 3 $-OR_2$, $-CON(R_2)(R_2)$,
 $-C(O)OR_2$, 1 to 3 C_1 - C_4 alkyl, $-S(O)_mR_2$, or 1H-tetrazol-5-yl;

Y is selected from: hydrogen, C_1 - C_{10} alkyl, $-(CH_2)_taryl$,
 $-(CH_2)_q(C_3$ - C_7 cycloalkyl), $-(CH_2)_qK$ - $(C_1$ - C_6 alkyl),
20 $-(CH_2)_qK$ - $(CH_2)_taryl$, $-(CH_2)_qK$ - $(CH_2)_t(C_3$ - C_7 cycloalkyl
containing O, NR_2 , S), and $-(CH_2)_qK$ - $(CH_2)_t(C_3$ - C_7 cycloalkyl), where
K is O, $S(O)_m$, $C(O)NR_2$, $CH=CH$, $C\equiv C$, $N(R_2)C(O)$, $C(O)NR_2$, $C(O)O$,
or $OC(O)$, and where the alkyl, R_2 , $(CH_2)_q$ and $(CH_2)_t$ groups may be
optionally substituted by C_1 - C_4 alkyl, hydroxyl, C_1 - C_4 lower alkoxy,
25 carboxyl, $-CONH_2$ or carboxylate C_1 - C_4 alkyl esters, and aryl is phenyl,
naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl,
pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiophenyl,
quinolinyl, pyrazinyl, or isothiazolyl which is optionally substituted by 1
to 3 halogen, 1 to 3 $-OR_2$, $-C(O)OR_2$, $-C(O)N(R_2)(R_2)$, nitro, cyano,
30 benzyl, 1 to 3 C_1 - C_4 alkyl, $-S(O)_mR_2$, or 1H-tetrazol-5-yl;

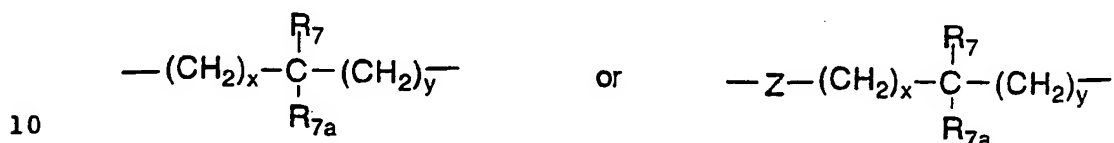
R_4 and R_5 are independently hydrogen, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1 - C_{10} alkanoyloxy, 1 to 3 C_1 - C_6 alkoxy, phenyl, phenoxy, 2-

- 12 -

furyl, C₁-C₆ alkoxy carbonyl, S(O)_m(C₁-C₆ alkyl); or R₄ and R₅ can be taken together to form -(CH₂)_dL_a(CH₂)_e- where L_a is C(R₂)₂, O, S(O)_m or N(R₂), d and e are independently 1 to 3 and R₂ is as defined above;

5

A is:



10

where x and y are independently 0, 1, 2 or 3;

15

Z is N-R_{6a} or O, where R_{6a} is hydrogen or C₁-C₆ alkyl;

20

R₆ is hydrogen, C₁-C₆ alkyl, or (CH₂)_varyl, wherein the alkyl and (CH₂)_v groups may be optionally substituted by 1-2 O(R₂), S(O)_mR₂, 1H-tetrazol-5-yl, C(O)OR₂, C(O)N(R₂)(R₂) or SO₂N(R₂)(R₂), N(R₂)C(O)N(R₂)(R₂), and wherein aryl is phenyl, pyridyl, 1H-tetrazol-5-yl, triazolyl, imidazolyl, thiazolyl, pyrazolyl, thiadiazolyl, imidazolone-1-yl, benzimidazol-2-yl, triazolinone-yl optionally substituted with C₁-C₆ alkyl, C₃-C₆ cycloalkyl, amino, or hydroxyl;

25

R₇ and R_{7a} are independently hydrogen, C₁-C₆ alkyl, trifluoromethyl, phenyl, substituted C₁-C₆ alkyl where the substituents are imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)_mR₂, C(O)O(C₁-C₆ alkyl), C₃-C₇ cycloalkyl, N(R₂)(R₂), C(O)N(R₂)(R₂); or R₇ and R_{7a} can independently be joined to one or both of R₄ and R₅ groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R₇ or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms; or R₇ and R_{7a} can be joined to one another to form a C₃-C₇ cycloalkyl;

30

l is 0, 1 or 2;

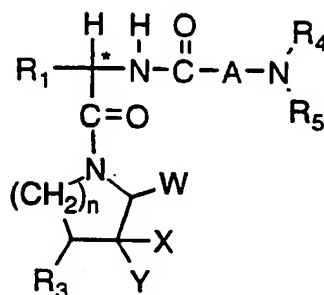
m is 0, 1, or 2;

- 13 -

n is 1, 2, or 3;
 q is 0, 1, 2, 3, or 4;
 r is 0, 1, 2, or 3;
 t is 0, 1, 2, or 3;
 v is 0, 1, or 2 ;

and pharmaceutically acceptable salts and individual diastereomers thereof.

Preferred compounds within this first embodiment include those of Formula AIa:



Formula AIa

wherein:

R₁ is selected from the group consisting of:

C₁-C₁₀ alkyl, aryl (C₁-C₄ alkyl)-, C₃-C₆ cycloalkyl (C₁-C₄ alkyl)-, (C₁-C₄ alkyl)-K-(C₁-C₂ alkyl)-, aryl (C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-, and (C₃-C₇ cycloalkyl)(C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-, where K is O, S(O)_m, OC(O), C(O)O and the alkyl groups may be further substituted by 1 to 7 halogen, S(O)_mR₂, 1 to 3 OR₂ or C(O)OR₂ and aryl is phenyl, naphthyl, indolyl, pyridyl, benzothienyl, or benzofuranyl which may be further substituted by 1-2 C₁-C₄ alkyl, 1 to 2 halogen, 1 to 2 OR₂, S(O)_mR₂ or C(O)OR₂;

R₂ is hydrogen, C₁-C₆ alkyl, or C₃-C₇ cycloalkyl and where two C₁-C₆ alkyl groups are present on one atom they may be optionally joined to form a C₄-C₇ cyclic ring optionally including oxygen, sulfur or NR_{3a};

- 14 -

R₃ is hydrogen or phenyl optionally substituted in the ortho position by a C₁-C₆ alkyl group, -NHSO₂CF₃, -(CH₂)_r (1H-tetrazol-5-yl), -(CH₂)_rC(O)OR₂, (CH₂)_rC(O)N(R₂)(R₆);

5 R_{3a} is hydrogen, or C₁-C₄ alkyl;

W is -CN, -C(O)OR₂, -C(O)N(R₂)(R₂), -C(O)N(R₂)(CH₂)_l phenyl, 1H-tetrazol-5-yl, or -(CH₂)_rOR₂;

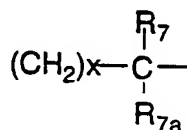
10 X is hydrogen, -(CH₂)_qC(O)N(R₂)(R₆), or -(CH₂)_qC(O)OR₂;

Y is hydrogen, C₁-C₈ alkyl, -(CH₂)_t phenyl, -(CH₂)_t pyridyl, or -(CH₂)_tthiazolyl;

15 R₄ and R₅ are independently hydrogen, C₁-C₆ alkyl, or substituted C₁-C₆ alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxyl, S(O)_m (C₁-C₆ alkyl) or phenyl;

20 R₆ is hydrogen, or C₁-C₆ alkyl;

A is:



25

where x is 0, or 1;

R₇ and R_{7a} are independently hydrogen C₁-C₆ alkyl, trifluoromethyl, phenyl, substituted C₁-C₆ alkyl where the substituents are imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)_mR₂, C(O)O(C₁-C₆ alkyl), C₅-C₇ cycloalkyl, N(R₂)(R₂), C(O)N(R₂)(R₂); or R₇ and R_{7a} can
 30 independently be joined to one of R₄ or R₅ to form alkylene bridges between the terminal nitrogen and the alkyl portion of R₇ or R_{7a} groups to form 5 or 6 membered rings; or R₇ and R_{7a} can be joined to one another to form a C₃ cycloalkyl;

- 15 -

l is 0 or 1;

n is 2;

m is 0, 1, or 2;

5 r is 0, 1, 2 or 3;

q is 0 or 1

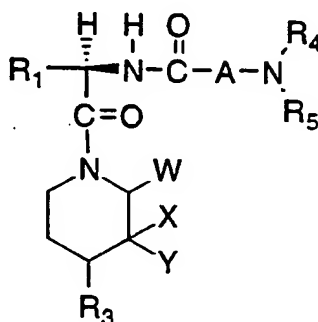
t is 0 or 1;

and pharmaceutically acceptable salts and individual diastereomers thereof.

10

More preferred compounds within this first embodiment include those of Formula AIb:

15



20

Formula AIb

wherein:

R₁ is selected from the group consisting of: C₁-C₁₀ alkyl, aryl (C₁-C₃ alkyl)-, and aryl (C₀-C₁ alkyl)-K-(C₁-C₂ alkyl)-, where K is O or S(O)_m and the aryl is phenyl, pyridyl, naphthyl, or indolyl which are optionally substituted by 1-2 C₁-C₄ alkyl, 1 to 2 halogen, 1 to 2 OR₂, S(O)_m R₂ or C(O)OR₂;

25

R₂ is hydrogen, C₁-C₆ alkyl, or C₃-C₇ cycloalkyl and where two C₁-C₆ alkyl groups are present on one atom they may be optionally joined to form a C₅-C₇ cyclic ring optionally including oxygen, sulfur or NR_{3a};

30

R₃ is hydrogen or phenyl optionally substituted in the ortho position by a C₁-C₃ alkyl group, (CH₂)_r(1H-tetrazol-5-yl) or (CH₂)_rC(O)OR₂;

- 16 -

R_{3a} is hydrogen, or C₁-C₄ alkyl;

W is -CN, -C(O)OR₂, or -C(O)N(R₂)R₂;

5

X is hydrogen or C(O)OR₂;

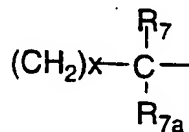
Y is hydrogen, benzyl, picoyl, or thiazolylmethyl;

10

R₄ and R₅ are independently hydrogen, C₁-C₃ alkyl, substituted C₁-C₃ alkyl where the substituents may be 1 to 2 hydroxyl;

A is

15



where x is 0, or 1;

20

R₇ and R_{7a} are independently hydrogen or C₁-C₄ alkyl;

m is 0, 1, or 2;

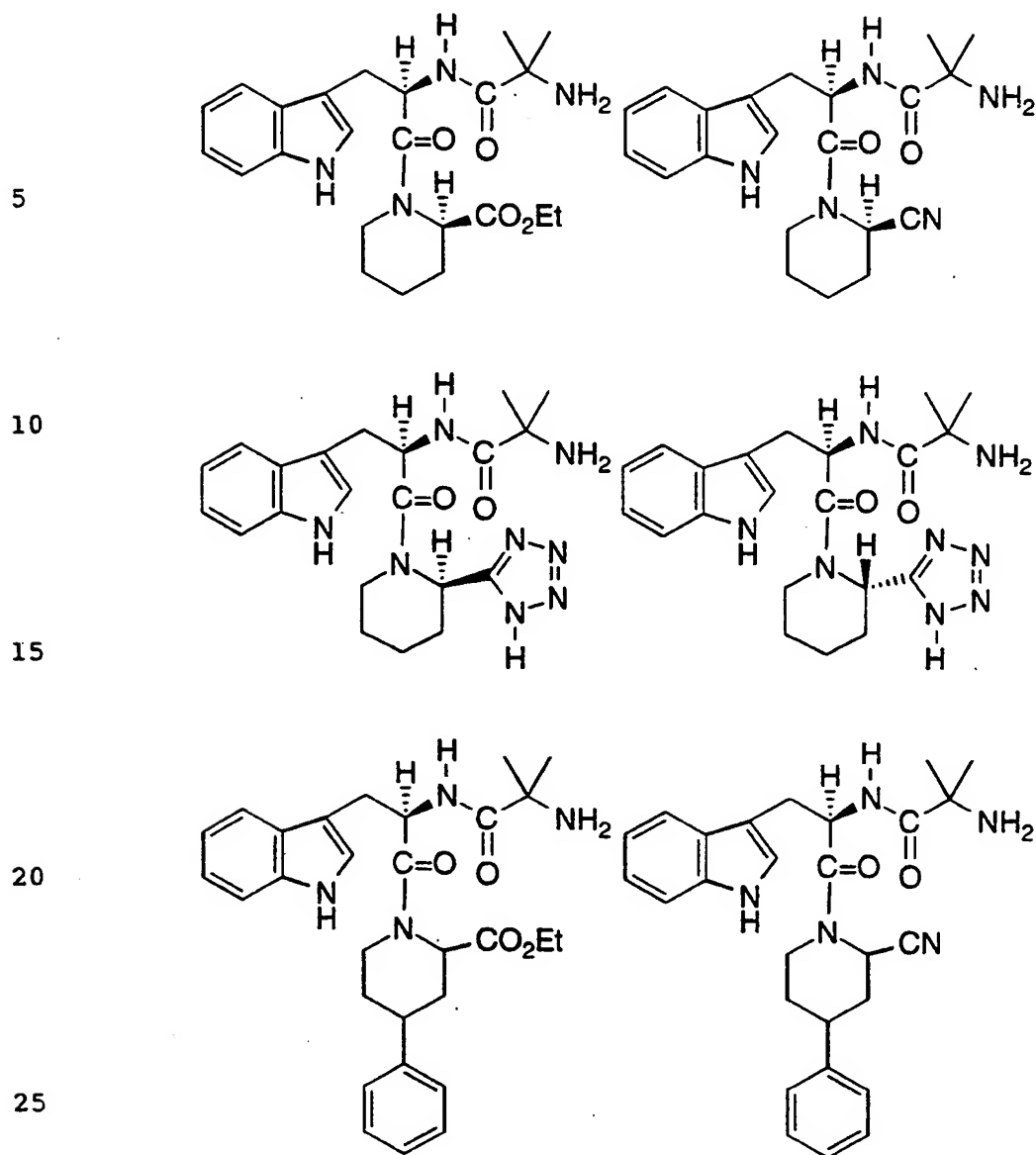
r is 0, 1, or 2;

25

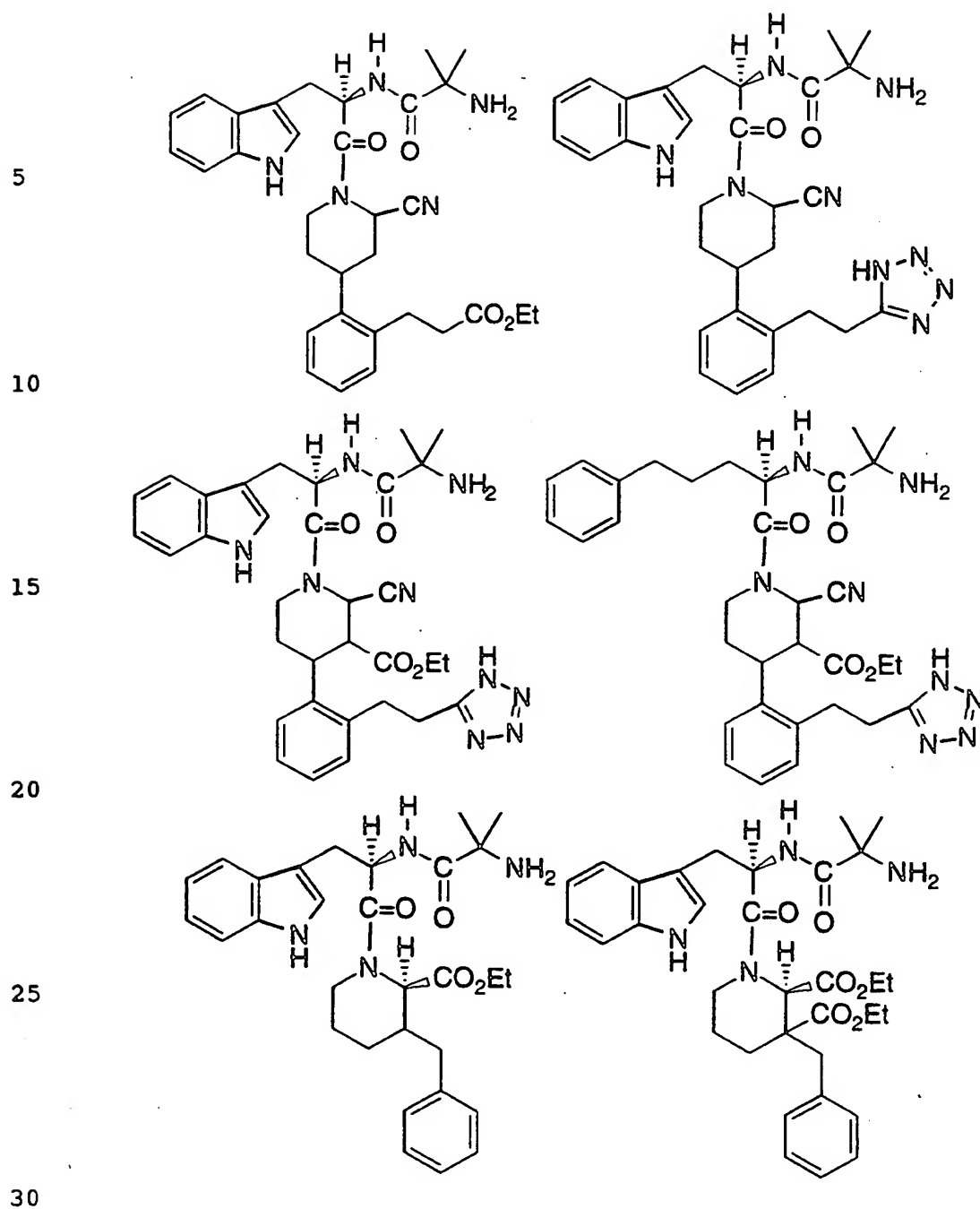
and pharmaceutically acceptable salts and individual diastereomers thereof.

The most preferred growth hormone releasing
30 compounds within this first embodiment include the following:

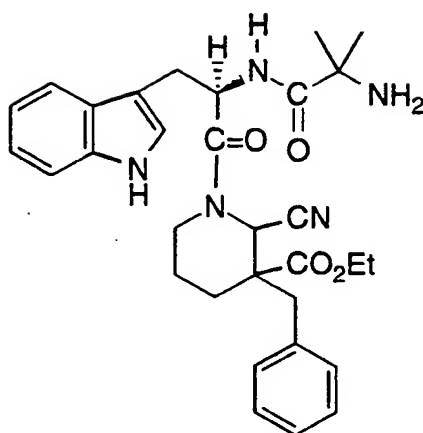
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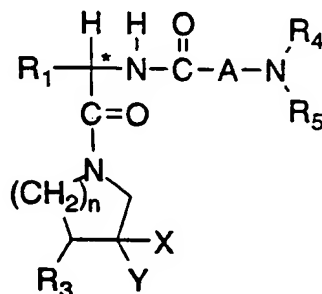


- 19 -



and pharmaceutically acceptable salts and individual diastereomers thereof.

A second embodiment of the present invention is directed to the compounds of the structural formula BI:



Formula BI

wherein:

R₁ is selected from the group consisting of:

C₁-C₁₀ alkyl, aryl, aryl(C₁-C₆ alkyl), (C₃-C₇ cycloalkyl)(C₁-C₆ alkyl)-, (C₁-C₅ alkyl)-K-(C₁-C₅ alkyl)-, aryl(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, and (C₃-C₇ cycloalkyl)(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, where K is O,

S(O)_m, N(R₂)C(O), C(O)N(R₂), OC(O), C(O)O, -CR₂=CR₂-, or -C≡C-, where aryl is selected from: phenyl, naphthyl, indolyl, azaindole, pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl, and R₂ and alkyl may be further substituted by 1 to 9 halogen, S(O)_mR_{2a}, 1 to 3 of OR_{2a} or C(O)OR_{2a}, and aryl may be further substituted by 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of OR₂, methylenedioxy,

- 20 -

-S(O)_mR₂, 1 to 2 of -CF₃, -OCF₃, nitro, -N(R₂)C(O)(R₂), -C(O)OR₂, -C(O)N(R₂)(R₂), -1H-tetrazol-5-yl, -SO₂N(R₂)(R₂), -N(R₂)SO₂ phenyl, or -N(R₂)SO₂R₂;

- 5 R₂ is selected from: hydrogen, C₁-C₆ alkyl, and C₃-C₇ cycloalkyl, and where two C₁-C₆ alkyl groups are present on one atom, they may be optionally joined to form a C₃-C₈ cyclic ring, optionally including oxygen, sulfur or NR_{3a}, where R_{3a} is hydrogen, or C₁-C₆ alkyl, optionally substituted by hydroxyl;
- 10 R_{2a} is hydrogen, or C₁-C₆ alkyl optionally substituted by hydroxyl;

R₃ is selected from: -(CH₂)_rphenyl, -(CH₂)_rnaphthyl, -C₁-C₁₀ alkyl, -C₃-C₇ cycloalkyl, and the phenyl, naphthyl and C₃-C₇ cycloalkyl rings may be substituted by 1 to 3 substituents selected from the group

15 consisting of: C₁-C₆ alkyl, halogen, -OR₂, -NHSO₂CF₃, -(CH₂)_rOR₆, -(CH₂)_rN(R₂)(R₆), -(CH₂)_r(R₆), -(CH₂)_rC(O)OR₂, -(CH₂)_rC(O)OR₆, -(CH₂)_rOC(O)R₂, -(CH₂)_rOC(O)R₆, -(CH₂)_rC(O)R₂, -(CH₂)_rC(O)R₆, -(CH₂)_rC(O)N(R₂)(R₂), -(CH₂)_rC(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)R₂, -(CH₂)_rN(R₂)C(O)R₆, -(CH₂)_rN(R₆)C(O)R₂, -(CH₂)_rN(R₆)C(O)R₆,

20 -(CH₂)_rN(R₂)C(O)OR₂, -(CH₂)_rN(R₂)C(O)OR₆, -(CH₂)_rN(R₆)C(O)OR₂, -(CH₂)_rN(R₆)C(O)OR₆, -(CH₂)_rN(R₂)C(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)N(R₂)(R₂), -(CH₂)_rN(R₆)C(O)N(R₂)(R₆), (CH₂)_rN(R₂)SO₂R₆, -(CH₂)_rN(R₂)SO₂R₂, -(CH₂)_rN(R₆)SO₂R₂, (CH₂)_rN(R₆)SO₂R₆,

25 -(CH₂)_rOC(O)N(R₂)(R₆), -(CH₂)_rOC(O)N(R₂)(R₂), -(CH₂)_rSO₂N(R₂)(R₆), -(CH₂)_rSO₂N(R₂)(R₂), (CH₂)_rSO₂NHC(O)R₆, -(CH₂)_rSO₂NHC(O)R₂, -(CH₂)_rSO₂NHC(O)OR₆, -(CH₂)_rSO₂NHC(O)OR₂, -(CH₂)_rC(O)NHC(O)NR₂, -(CH₂)_rC(O)NHC(O)NR₆, -(CH₂)_rC(O)NHC(O)R₂,

30 -(CH₂)_rCONHC(O)R₆, -(CH₂)_rCONHSO₂R₆, -(CH₂)_rCONHSO₂R₂, -(CH₂)_rCONHSO₂N(R₂)R₂, -(CH₂)_rCONHSO₂N(R₂)R₆, -(CH₂)_rN(R₂)SO₂N(R₂)R₆, -(CH₂)_rN(R₆)SO₂N(R₂)R₆, -(CH₂)_rS(O)_mR₆, and -(CH₂)_rS(O)_mR₂;

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R_{3a} is hydrogen, or C₁-C₆ alkyl optionally substituted by hydroxyl;

X is selected from: hydrogen, -C≡N, -(CH₂)_qN(R₂)C(O)R₂,
 -(CH₂)_qN(R₂)C(O)(CH₂)_taryl, -(CH₂)_qN(R₂)SO₂(CH₂)_taryl,
 5 -(CH₂)_qN(R₂)SO₂R₂, -(CH₂)_qN(R₂)C(O)N(R₂)(CH₂)_taryl,
 -(CH₂)_qN(R₂)C(O)N(R₂)(R₂), -(CH₂)_qC(O)N(R₂)(R₂),
 -(CH₂)_qC(O)N(R₂)(CH₂)_taryl, -(CH₂)_qC(O)OR₂,
 -(CH₂)_qC(O)O(CH₂)_taryl, -(CH₂)_qOR₂, -(CH₂)_qOC(O)R₂,
 -(CH₂)_qOC(O)(CH₂)_taryl, -(CH₂)_qOC(O)N(R₂)(CH₂)_taryl,
 10 -(CH₂)_qOC(O)N(R₂)(R₂), -(CH₂)_qC(O)R₂, -(CH₂)_qC(O)(CH₂)_taryl,
 -(CH₂)_qN(R₂)C(O)OR₂, -(CH₂)_qN(R₂)SO₂N(R₂)(R₂),
 -(CH₂)_qS(O)_mR₂, and -(CH₂)_qS(O)_m(CH₂)_taryl, where an R₂, (CH₂)_q
 and (CH₂)_t group may be optionally substituted by 1 to 2 C₁-C₄ alkyl,
 hydroxyl, C₁-C₄ lower alkoxy, carboxyl, CONH₂, S(O)_mCH₃,
 15 carboxylate C₁-C₄ alkyl esters, or 1H-tetrazol-5-yl, and aryl is phenyl,
 naphthyl, pyridyl, thiazolyl, or 1H-tetrazol-5-yl groups which may be
 optionally substituted by 1 to 3 halogen, 1 to 3 -OR₂, -CON(R₂)(R₂),
 -C(O)OR₂, 1 to 3 C₁-C₄ alkyl, -S(O)_mR₂, or 1H-tetrazol-5-yl;

20 Y is selected from: hydrogen, C₁-C₁₀ alkyl, -(CH₂)_taryl,
 -(CH₂)_q(C₃-C₇ cycloalkyl), -(CH₂)_q-K-(C₁-C₆ alkyl),
 -(CH₂)_q-K-(CH₂)_taryl, -(CH₂)_q-K-(CH₂)_t(C₃-C₇ cycloalkyl
 containing O, NR₂, S), and -(CH₂)_q-K-(CH₂)_t(C₃-C₇ cycloalkyl), where
 K is O, S(O)_m, C(O)NR₂, CH=CH, C≡C, N(R₂)C(O), C(O)NR₂, C(O)O,
 25 or OC(O), and where the alkyl, R₂, (CH₂)_q and (CH₂)_t groups may be
 optionally substituted by C₁-C₄ alkyl, hydroxyl, C₁-C₄ lower alkoxy,
 carboxyl, -CONH₂ or carboxylate C₁-C₄ alkyl esters, and aryl is phenyl,
 naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl,
 pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiophenyl,
 30 quinolinyl, pyrrazinyl, or isothiazolyl which is optionally substituted by 1
 to 3 halogen, 1 to 3 -OR₂, 1 to 2 -N(R₂)(R₂), -C(O)OR₂,
 -C(O)N(R₂)(R₂), nitro, -NHC(O)R₂, cyano, benzyl, 1 to 3 C₁-C₄ alkyl,
 -S(O)_mR₂, or 1H-tetrazol-5-yl;

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R4 and R5 are independently hydrogen, C1-C6 alkyl, substituted C1-C6 alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C1-C10 alkanoyloxy, 1 to 3 C1-C6 alkoxy, phenyl, phenoxy, 2-furyl, C1-C6 alkoxy carbonyl, S(O)_m(C1-C6 alkyl); or R4 and R5 can
 5 be taken together to form -(CH₂)_dL_a(CH₂)_e- where L_a is C(R₂)₂, O, S(O)_m or N(R₂), d and e are independently 1 to 3 and R₂ is as defined above;

A is:
 10



15 where x and y are independently 0, 1, 2 or 3;

Z is N-R_{6a} or O, where R_{6a} is hydrogen or C1-C6 alkyl;

20 R₆ is hydrogen, C1-C6 alkyl, or (CH₂)_varyl, wherein the alkyl and (CH₂)_v groups may be optionally substituted by 1-2 O(R₂), S(O)_mR₂, 1H-tetrazol-5-yl, C(O)OR₂, C(O)N(R₂)(R₂) or SO₂N(R₂)(R₂), N(R₂)C(O)N(R₂)(R₂), and wherein aryl is phenyl, pyridyl, 1H-tetrazol-5-yl, triazolyl, imidazolyl, thiazolyl, pyrazolyl, thiadiazolyl, imidazolone-
 25 1-yl, oxadiazolyl, benzimidazol-2-yl, triazolinone-yl, optionally substituted with C1-C6 alkyl, C3-C6 cycloalkyl, amino, or hydroxyl;

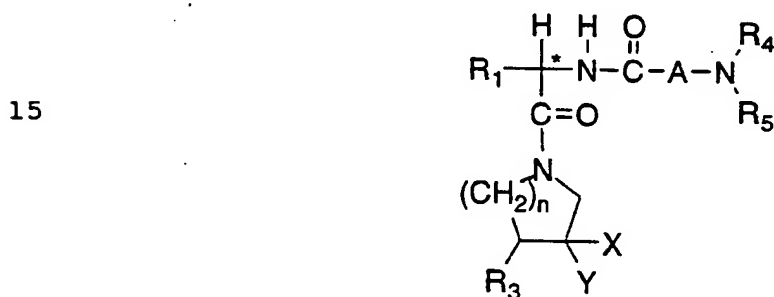
R₇ and R_{7a} are independently hydrogen, C1-C6 alkyl, trifluoromethyl, phenyl, substituted C1-C6 alkyl where the substituents are imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)_mR₂, C(O)OR₂, C3-C7
 30 cycloalkyl, N(R₂)(R₂), C(O)N(R₂)(R₂); or R₇ and R_{7a} can independently be joined to one or both of R₄ and R₅ groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R₇ or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms; or R₇ and R_{7a} can be joined to one another to form a C3-C7 cycloalkyl;

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m is 0, 1, or 2;
 n is 1, 2, or 3;
 q is 0, 1, 2, 3 or 4;
 r is 0, 1, 2, or 3;
 t is 0, 1, 2, or 3;
 v is 0, 1, or 2 ;

and pharmaceutically acceptable salts and individual diastereomers thereof.

Preferred compounds within this second embodiment include those of Formula BIa:



Formula BIa

wherein:

R₁ is selected from the group consisting of:

C₁-C₁₀ alkyl, aryl (C₁-C₄ alkyl)-, C₃-C₆ cycloalkyl (C₁-C₄ alkyl)-,
 (C₁-C₄ alkyl)-K-(C₁-C₂ alkyl)-, aryl (C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-,
 and (C₃-C₇ cycloalkyl)(C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-, where K is O,
 S(O)_m, OC(O), or C(O)O, and the alkyl groups may be further
 substituted by 1 to 7 halogen, S(O)_mR₂, 1 to 3 OR₂ or C(O)OR₂, and
 aryl is phenyl, naphthyl, indolyl, pyridyl, benzimidazolyl, azaindoleyl,
 benzothienyl or benzofuranyl which may be further substituted by 1-2
 C₁-C₄ alkyl, 1 to 2 halogen, 1 to 2 -OR₂, -S(O)_mR₂, or -C(O)OR₂;

R₂ is hydrogen, C₁-C₆ alkyl, C₃-C₇ cycloalkyl and where two C₁-C₆
 alkyl groups are present on one atom they may be optionally joined to
 form a C₄-C₇ cyclic ring optionally including oxygen, sulfur or NR_{3a};

- 24 -

R₃ is phenyl which is optionally substituted by 1 to 2 C₁-C₆ alkyl groups, 1 to 2 halogen, or 1 to 2 -OR₂, and which may be further substituted in the ortho position by a substituent selected from the group consisting of:

5 -NHSO₂CF₃, -(CH₂)_rOR₆, -(CH₂)_rN(R₂)(R₆), -(CH₂)_r(R₆),
 -(CH₂)_rC(O)OR₂, -(CH₂)_rC(O)OR₆, -(CH₂)_rOC(O)R₂,
 -(CH₂)_rOC(O)R₆, -(CH₂)_rC(O)R₂, -(CH₂)_rC(O)R₆,
 -(CH₂)_rC(O)N(R₂)(R₂), -(CH₂)_rC(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)R₂
 10 -(CH₂)_rN(R₂)C(O)R₆, -(CH₂)_rN(R₆)C(O)R₂, -(CH₂)_rN(R₆)C(O)R₆,
 -(CH₂)_rN(R₂)C(O)OR₂, -(CH₂)_rN(R₂)C(O)OR₆,
 -(CH₂)_rN(R₆)C(O)OR₂, -(CH₂)_rN(R₆)C(O)OR₆,
 -(CH₂)_rN(R₂)C(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)N(R₂)(R₂),
 -(CH₂)_rN(R₆)C(O)N(R₂)(R₆), (CH₂)_rN(R₂)SO₂R₆,
 15 -(CH₂)_rN(R₂)SO₂R₂, -(CH₂)_rN(R₆)SO₂R₂, (CH₂)_rN(R₆)SO₂R₆,
 -(CH₂)_rOC(O)N(R₂)(R₆), -(CH₂)_rOC(O)N(R₂)(R₂),
 -(CH₂)_rSO₂N(R₂)(R₆), -(CH₂)_rSO₂N(R₂)(R₂), (CH₂)_rSO₂NHC(O)R₆,
 -(CH₂)_rSO₂NHC(O)R₂, -(CH₂)_rSO₂NHC(O)OR₆,
 -(CH₂)_rSO₂NHC(O)OR₂, -(CH₂)_rC(O)NHC(O)NR₂,
 20 -(CH₂)_rC(O)NHC(O)NR₆, -(CH₂)_rC(O)NHC(O)R₂,
 -(CH₂)_rCONHC(O)R₆, -(CH₂)_rCONHSO₂R₆, -(CH₂)_rCONHSO₂R₂,
 -(CH₂)_rCONHSO₂N(R₂)R₂, -(CH₂)_rCONHSO₂N(R₂)R₆,
 -(CH₂)_rN(R₂)SO₂N(R₂)R₆, -(CH₂)_rN(R₆)SO₂N(R₂)R₆,
 25 -(CH₂)_rS(O)_mR₆, and -(CH₂)_rS(O)_mR₂;

R_{3a} is hydrogen, or C₁-C₄ alkyl;

X is selected from: hydrogen, -(CH₂)_qN(R₂)C(O)R₂,
 -(CH₂)_qN(R₂)C(O)(CH₂)_taryl, -(CH₂)_qN(R₂)C(O)OR₂,
 30 -(CH₂)_qN(R₂)SO₂(CH₂)_taryl, -(CH₂)_qN(R₂)SO₂R₂,
 -(CH₂)_qN(R₂)C(O)N(R₂)(CH₂)_taryl, -(CH₂)_qN(R₂)C(O)N(R₂)(R₂),
 -(CH₂)_qC(O)N(R₂)(R₂), -(CH₂)_qC(O)N(R₂)(CH₂)_taryl,
 -(CH₂)_qC(O)OR₂, -(CH₂)_qC(O)O(CH₂)_taryl, -(CH₂)_qOC(O)R₂,
 -(CH₂)_qOC(O)(CH₂)_taryl, -(CH₂)_qS(O)_mR₂, and

- 25 -

$-(CH_2)_qS(O)_m(CH_2)_t$ aryl, where an R_2 group may be optionally substituted by hydroxyl, carboxyl, $CONH_2$, $S(O)_mCH_3$, carboxylate C_1 - C_4 alkyl esters, or tetrazole and the aryl which is phenyl, naphthyl, pyridyl or 1-H-tetrazolyl may be optionally substituted by 1 to 2 halogen,
 5 1 to 2 $-OR_2$, $-CONH_2$, $-C(O)OR_2$, 1 to 3 C_1 - C_4 alkyl, $-S(O)_mR_2$, or 1H-tetrazole-5-yl;

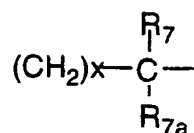
Y is selected from: hydrogen, C_1 - C_8 alkyl, $(CH_2)_t$ aryl, $-(CH_2)_q(C_5$ - C_6 cycloalkyl), $-(CH_2)_q$ -K- $(C_1$ - C_6 alkyl), $-(CH_2)_q$ -K- $(CH_2)_t$ aryl,
 10 $-(CH_2)_q$ -K- $(CH_2)_t$ (C_3 - C_7 cycloalkyl containing O, NR_2 , or S), and $-(CH_2)_q$ -K- $(CH_2)_t$ (C_5 - C_6 cycloalkyl), where K is O or $S(O)_m$ and where the alkyl groups may be optionally substituted by hydroxyl, carboxyl, $CONH_2$, carboxylate C_1 - C_4 alkyl esters or 1H-tetrazole-5-yl and the aryl which is phenyl, naphthyl, pyridyl, 1-H-tetrazolyl, thiazolyl,
 15 imidazolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl or thiopheneyl is optionally substituted by 1 to 3 halogen, 1 to 3 $-OR_2$, 1 to 2 $-N(R_2)(R_2)$, $-C(O)OR_2$, $-C(O)N(R_2)(R_2)$, cyano, 1 to 2 C_1 - C_4 alkyl, benzyl, $-S(O)_mR_2$, or 1H-tetrazol-5-yl;

20 R_4 and R_5 are independently hydrogen, C_1 - C_6 alkyl, or substituted C_1 - C_6 alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxyl, $S(O)_m$ (C_1 - C_6 alkyl) or phenyl;

25 R_6 is H, C_1 - C_6 alkyl, or $(CH_2)_v$ aryl, wherein the $(CH_2)_v$ and alkyl groups may be optionally substituted by 1-2 $O(R_2)$, $S(O)_mR_2$, $C(O)OR_2$, $C(O)N(R_2)(R_2)$ or $SO_2N(R_2)(R_2)$, $N(R_2)C(O)N(R_2)(R_2)$, wherein the aryl group could be phenyl, pyridyl, 1H-tetrazol-5-yl, triazolyl, imidazolyl, thiazolyl, oxadiazolyl, pyrazolyl, thiadiazolyl, benzimidazol-2-yl, optionally substituted with C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, amino,
 30 or hydroxyl;

A is:

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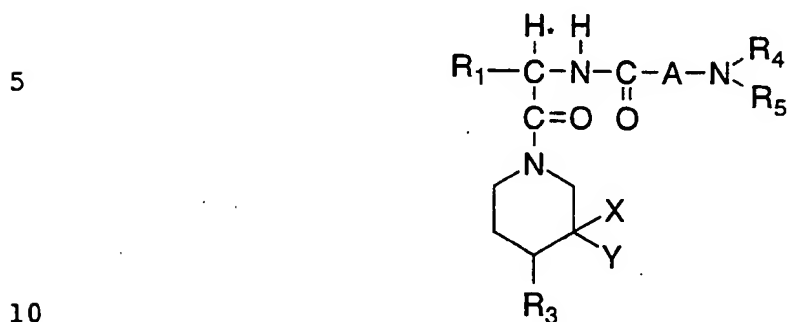
- 5 where x is 0, or 1;
 R₇ and R_{7a} are independently hydrogen C₁-C₆ alkyl, trifluoromethyl, phenyl, substituted C₁-C₆ alkyl where the substituents are imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)mR₂, C(O)OR₂, C₅-C₇ cycloalkyl, N(R₂)(R₂), C(O)N(R₂)(R₂); or R₇ and R_{7a} can
 10 independently be joined to one of R₄ or R₅ to form alkylene bridges between the terminal nitrogen and the alkyl portion of R₇ or R_{7a} groups to form 5 or 6 membered rings; or R₇ and R_{7a} can be joined to one another to form a C₃ cycloalkyl;
- 15 n is 2;
 m is 0, 1, or 2;
 r is 0, 1, 2, or 3;
 q is 0, 1, 2, or 3;
 t is 0, 1, 2, or 3;
 20 v is 0, 1, or 2,
 and pharmaceutically acceptable salts and individual diastereomers thereof.

25

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More preferred compounds within this second embodiment include those of Formula BIb:



Formula BIb

wherein:

R₁ is selected from the group consisting of: C₁-C₁₀ alkyl, aryl (C₁-C₃ alkyl)-, (C₃-C₇ cycloalkyl)(C₁-C₃ alkyl)-, and aryl (C₀-C₁ alkyl)-K-(C₁-C₂ alkyl)-, where K is O or S(O)_m and aryl is specifically phenyl, pyridyl, naphthyl, indolyl, azaindolyl, or benzimidazolyl which is optionally substituted by 1-2 C₁-C₄ alkyl, 1 to 2 halogen, 1 to 2 OR₂, S(O)_m R₂, or C(O)OR₂;

R₂ is hydrogen, C₁-C₆ alkyl, C₃-C₇ cycloalkyl and where two C₁-C₆ alkyl groups are present on one atom they may be optionally joined to form a C₅-C₇ cyclic ring optionally including oxygen, sulfur or NR_{3a};

R₃ is phenyl optionally substituted by 1 to 2 C₁-C₆ alkyl groups, 1 to 2 halogen or 1 to 2 OR₂, and which may be further substituted in the ortho position by a substituent selected from the group consisting of:

- NHSO₂CF₃, -(CH₂)_rOR₆, -(CH₂)_rN(R₂)(R₆), -(CH₂)_r(R₆),
- (CH₂)_rC(O)OR₆, -(CH₂)_rOC(O)R₂, -(CH₂)_rOC(O)R₆,
- (CH₂)_rC(O)R₂, -(CH₂)_rC(O)R₆, -(CH₂)_rC(O)N(R₂)(R₂),
- (CH₂)_rC(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)R₂, -(CH₂)_rN(R₂)C(O)R₆,
- (CH₂)_rN(R₆)C(O)R₂, -(CH₂)_rN(R₆)C(O)R₆, -(CH₂)_rN(R₂)C(O)OR₂,
- (CH₂)_rN(R₂)C(O)OR₆, -(CH₂)_rN(R₆)C(O)OR₂,
- (CH₂)_rN(R₆)C(O)OR₆, -(CH₂)_rN(R₂)C(O)N(R₂)(R₆),
- (CH₂)_rN(R₂)C(O)N(R₂)(R₂), -(CH₂)_rN(R₆)C(O)N(R₂)(R₆),

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$(\text{CH}_2)_r\text{N}(\text{R}_2)\text{SO}_2\text{R}_6$, $-(\text{CH}_2)_r\text{N}(\text{R}_2)\text{SO}_2\text{R}_2$, $-(\text{CH}_2)_r\text{N}(\text{R}_6)\text{SO}_2\text{R}_2$,
 $\text{CH}_2)_r\text{N}(\text{R}_6)\text{SO}_2\text{R}_6$, $-(\text{CH}_2)_r\text{OC}(\text{O})\text{N}(\text{R}_2)(\text{R}_6)$,
 $-(\text{CH}_2)_r\text{OC}(\text{O})\text{N}(\text{R}_2)(\text{R}_2)$, $-(\text{CH}_2)_r\text{SO}_2\text{N}(\text{R}_2)(\text{R}_6)$,
 $-(\text{CH}_2)_r\text{SO}_2\text{N}(\text{R}_2)(\text{R}_2)$, $(\text{CH}_2)_r\text{SO}_2\text{NHC}(\text{O})\text{R}_6$, $-(\text{CH}_2)_r\text{SO}_2\text{NHC}(\text{O})\text{R}_2$,
5 $-(\text{CH}_2)_r\text{SO}_2\text{NHC}(\text{O})\text{OR}_6$, $-(\text{CH}_2)_r\text{SO}_2\text{NHC}(\text{O})\text{OR}_2$,
 $-(\text{CH}_2)_r\text{CONHSO}_2\text{R}_6$, $-(\text{CH}_2)_r\text{CONHSO}_2\text{R}_2$, $-(\text{CH}_2)_r\text{S}(\text{O})_m\text{R}_6$, and
 $-(\text{CH}_2)_r\text{S}(\text{O})_m\text{R}_2$;

10 R_{3a} is hydrogen, or C₁-C₄ alkyl;

X is selected from: hydrogen, $-(\text{CH}_2)_q\text{N}(\text{R}_2)\text{C}(\text{O})\text{R}_2$,
 $-(\text{CH}_2)_q\text{N}(\text{R}_2)\text{C}(\text{O})(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_q\text{N}(\text{R}_2)\text{SO}_2(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_q$
 $\text{N}(\text{R}_2)\text{SO}_2\text{R}_2$, $-(\text{CH}_2)_q\text{N}(\text{R}_2)\text{C}(\text{O})\text{N}(\text{R}_2)(\text{CH}_2)_t\text{aryl}$,
 $-(\text{CH}_2)_q\text{N}(\text{R}_2)\text{C}(\text{O})\text{N}(\text{R}_2)(\text{R}_2)$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{N}(\text{R}_2)(\text{R}_2)$,
 15 $-(\text{CH}_2)_q\text{N}(\text{R}_2)\text{C}(\text{O})\text{OR}_2$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{N}(\text{R}_2)(\text{CH}_2)_t\text{aryl}$,
 $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}_2$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{O}(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_q\text{OC}(\text{O})\text{R}_2$,
 $-(\text{CH}_2)_q\text{OC}(\text{O})(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_q\text{S}(\text{O})_m\text{R}_2$, and
 $-(\text{CH}_2)_q\text{S}(\text{O})_m(\text{CH}_2)_t\text{aryl}$, where an R_2 group may be optionally
 substituted by hydroxyl, carboxyl, $-\text{CONH}_2$, $-\text{S}(\text{O})_m\text{CH}_3$, carboxylate
 20 C₁-C₄ alkyl esters or tetrazole and aryl is phenyl, naphthyl or pyridyl
 which may be further substituted by 1-2 halogen, 1 to 2 OR_2 , $\text{C}(\text{O})\text{OR}_2$,
 1 to 3 C₁-C₄ alkyl, $\text{S}(\text{O})_m\text{R}_2$, or 1H-tetrazole-5-yl;

Y is selected from: hydrogen, C₁-C₈ alkyl, $(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_q$ C₅-C₇
 25 cycloalkyl, $-(\text{CH}_2)_q\text{-K-(C}_1\text{-C}_6\text{ alkyl)}$, $-(\text{CH}_2)_q\text{-K-(CH}_2)_t\text{aryl}$, and
 $-(\text{CH}_2)_q\text{-K-(CH}_2)_t$ (C₅-C₆ cycloalkyl), where K is $\text{S}(\text{O})_m$ and where the
 alkyl groups may be optionally substituted by hydroxyl, carboxyl,
 CONH_2 , carboxylate C₁-C₄ alkyl esters or 1H-tetrazole-5-yl and aryl is
 specifically phenyl, naphthyl, pyridyl, thiazolyl, thiophenyl, pyrazolyl,
 30 oxazolyl, isoxazolyl or imidazolyl which may be optionally substituted
 by 1 to 2 halogen, 1 to 2 OR_2 , 1 to 2 $-\text{N}(\text{R}_2)(\text{R}_2)$, $-\text{CO}(\text{OR}_2)$, 1 to 2 C₁-
 C₄ alkyl, $\text{S}(\text{O})_m\text{R}_2$, or 1H-tetrazol-5-yl;

- 29 -

R₄ and R₅ are independently hydrogen, C₁-C₄ alkyl, substituted C₁-C₃ alkyl where the substituents may be 1 to 2 hydroxyl;

5 R₆ is hydrogen, C₁-C₆ alkyl or (CH₂)_varyl, wherein the C₁-C₆ alkyl and the (CH₂)_varyl groups may be optionally substituted by 1-2 O(R₂), S(O)_mR₂, C(O)OR₂, C(O)N(R₂)(R₂) or SO₂N(R₂)(R₂), N(R₂)C(O)N(R₂)(R₂), wherein aryl is specifically phenyl, pyridyl, 1H-tetrazol-5-yl, triazolyl, imidazolyl, thiazolyl, oxadiazolyl, pyrazolyl, thiadiazolyl, benzimidazol-2-yl, optionally substituted with C₁-C₆ alkyl,
10 C₃-C₆ cycloalkyl, amino, or hydroxyl;

A is



where x is 0, or 1;

20 R₇ and R_{7a} are independently hydrogen, C₁-C₂ alkyl, phenyl, substituted C₁-C₆ alkyl wherein the substituent is imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)_mR₂; or R₇ and R_{7a} can be independently be joined to one another to form a C₃ cycloalkyl;

25 m is 0, 1, or 2;

r is 0, 1, 2, or 3;

q is 0, 1, 2, or 3;

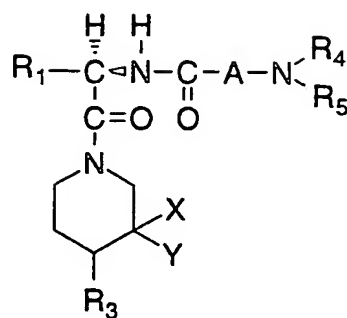
t is 0, 1, 2, or 3;

v is 0, 1, or 2;

30 and pharmaceutically acceptable salts and individual diastereomers thereof.

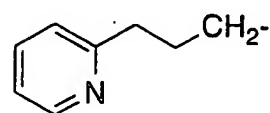
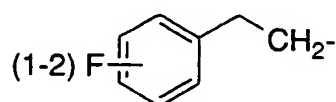
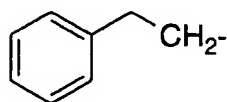
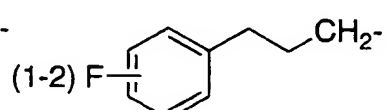
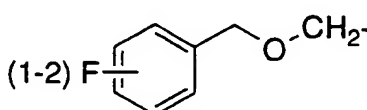
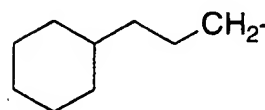
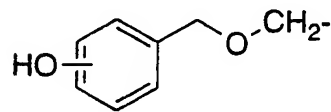
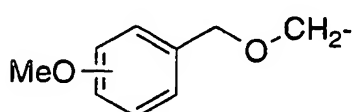
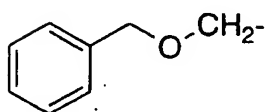
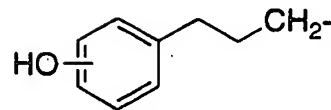
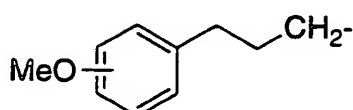
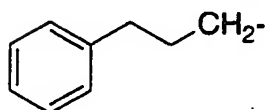
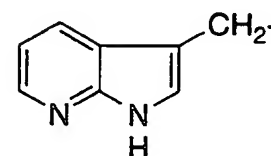
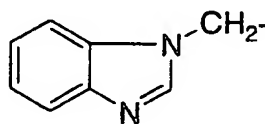
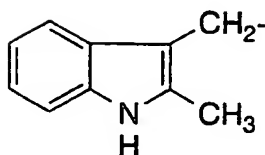
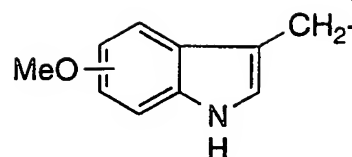
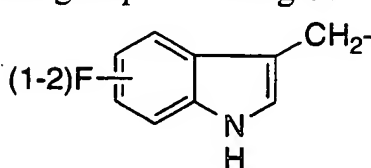
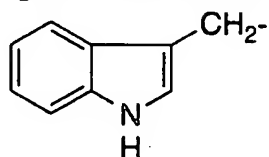
Still more preferred compounds within this second embodiment are realized in Formula B1c:

- 30 -



Formula BIc

wherein:

R₁ is selected from the group consisting of:

or their regioisomers where not specified;

- 31 -

R₂ is hydrogen, C₁-C₆ alkyl, or C₃-C₇ cycloalkyl and where two C₁-C₆ alkyl groups are present on one atom they may be optionally joined to form a C₅-C₇ cyclic ring optionally including oxygen, sulfur or NR_{3a};

5

R₃ is phenyl optionally substituted in the ortho position with a substituent selected from the group consisting of:

-NHSO₂CF₃, -(CH₂)_rOR₆, -(CH₂)_r(R₆), -(CH₂)_rC(O)OR₂,
 -(CH₂)_rC(O)OR₆, -(CH₂)_rOC(O)R₂, -(CH₂)_rOC(O)R₆,
 10 -(CH₂)_rC(O)R₂, -(CH₂)_rC(O)R₆, -(CH₂)_rC(O)N(R₂)(R₂),
 -(CH₂)_rC(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)R₂, -(CH₂)_rN(R₂)C(O)R₆,
 -(CH₂)_rN(R₆)C(O)R₂, -(CH₂)_rN(R₆)C(O)R₆, -(CH₂)_rN(R₂)C(O)OR₂,
 -(CH₂)_rN(R₂)C(O)OR₆, -(CH₂)_rN(R₆)C(O)OR₂,
 -(CH₂)_rN(R₆)C(O)OR₆, -(CH₂)_rN(R₂)C(O)N(R₂)(R₆),
 15 -(CH₂)_rN(R₂)C(O)N(R₂)(R₂), -(CH₂)_rN(R₆)C(O)N(R₂)(R₆),
 (CH₂)_rN(R₂)SO₂R₆, -(CH₂)_rN(R₂)SO₂R₂, -(CH₂)_rN(R₆)SO₂R₂,
 (CH₂)_rN(R₆)SO₂R₆, -(CH₂)_rOC(O)N(R₂)(R₆),
 -(CH₂)_rOC(O)N(R₂)(R₂), -(CH₂)_rSO₂N(R₂)(R₆),
 -(CH₂)_rSO₂N(R₂)(R₂), (CH₂)_rSO₂NHC(O)R₆, -(CH₂)_rSO₂NHC(O)R₂,
 20 -(CH₂)_rSO₂NHC(O)OR₆, -(CH₂)_rSO₂NHC(O)OR₂,
 -(CH₂)_rCONHSO₂R₆, -(CH₂)_rCONHSO₂R₂, -(CH₂)_rS(O)_mR₆, and
 -(CH₂)_rS(O)_mR₂;

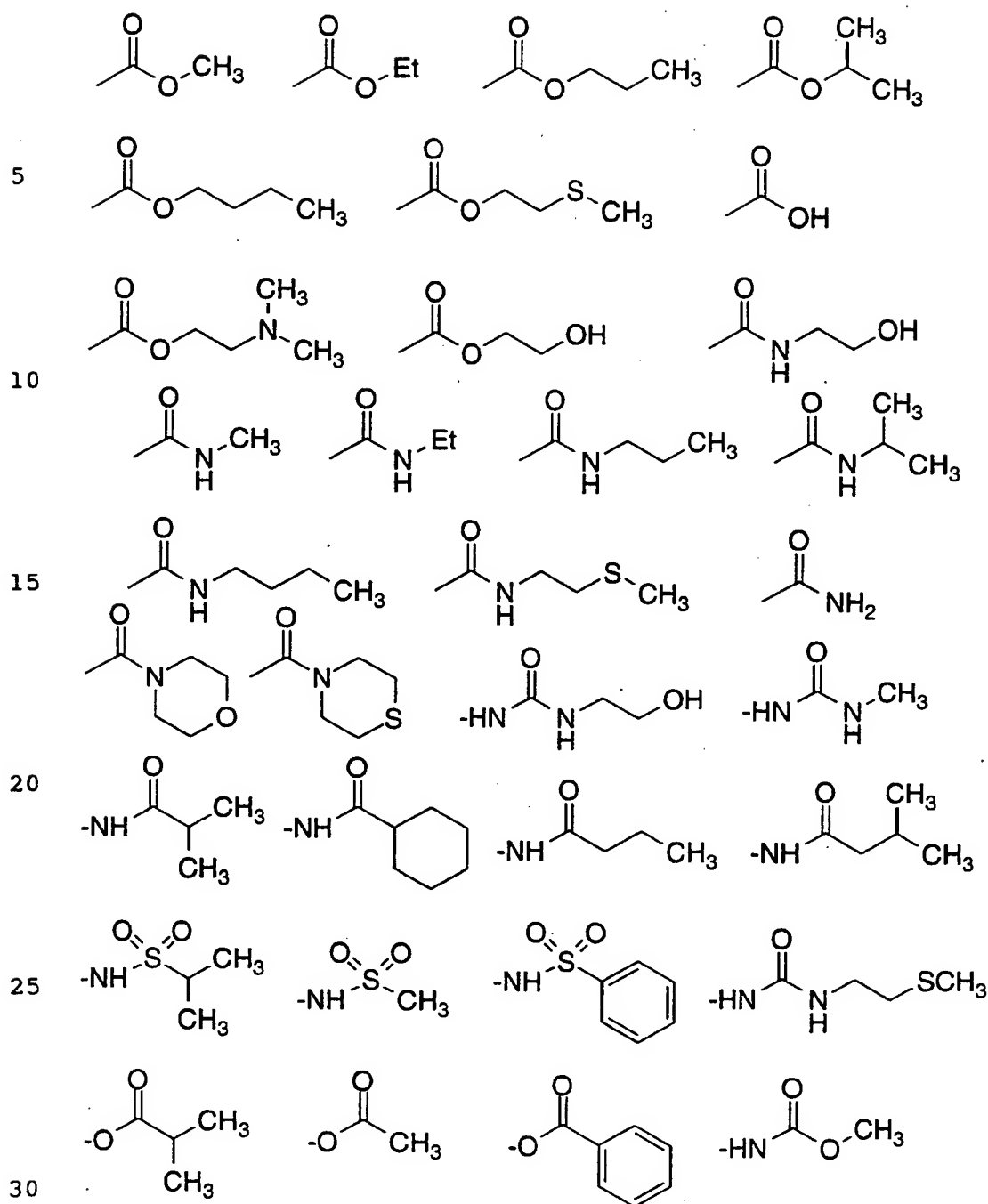
R_{3a} is hydrogen, or C₁-C₄ alkyl;

25

X is selected from the group consisting of: hydrogen,

30

- 32 -



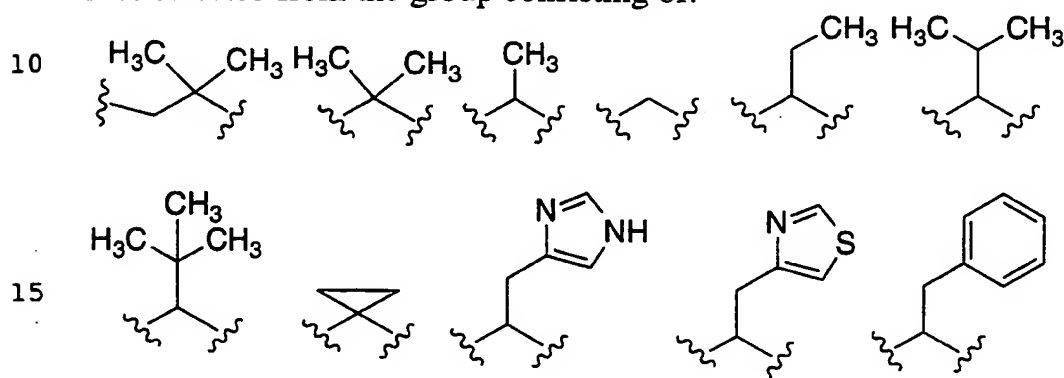
Y is selected from the group consisting of:

hydrogen, C₁-C₈ alkyl, (CH₂)_taryl, -(CH₂)_q C₅-C₇ cycloalkyl, -(CH₂)_q-K-(C₁-C₆ alkyl), -(CH₂)_q-K-(CH₂)_taryl, or -(CH₂)_q-K-(CH₂)_t (C₅-C₆ cycloalkyl) where K is S(O)_m and where the alkyl groups may be

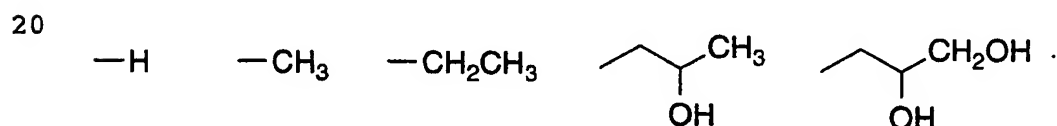
- 33 -

optionally substituted by hydroxyl, carboxyl, CONH₂, carboxylate C₁-C₄ alkyl esters or 1H-tetrazol-5-yl, and where aryl is specifically phenyl, naphthyl, pyridyl, thiazolyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrimidinyl, or imidazolyl, which may be
 5 optionally substituted by 1 to 2 halogen, 1 to 2 OR₂, CO(OR₂), 1 to 2 C₁-C₄ alkyl, S(O)_mR₂ or 1H-tetrazol-5-yl;

A is selected from the group consisting of:



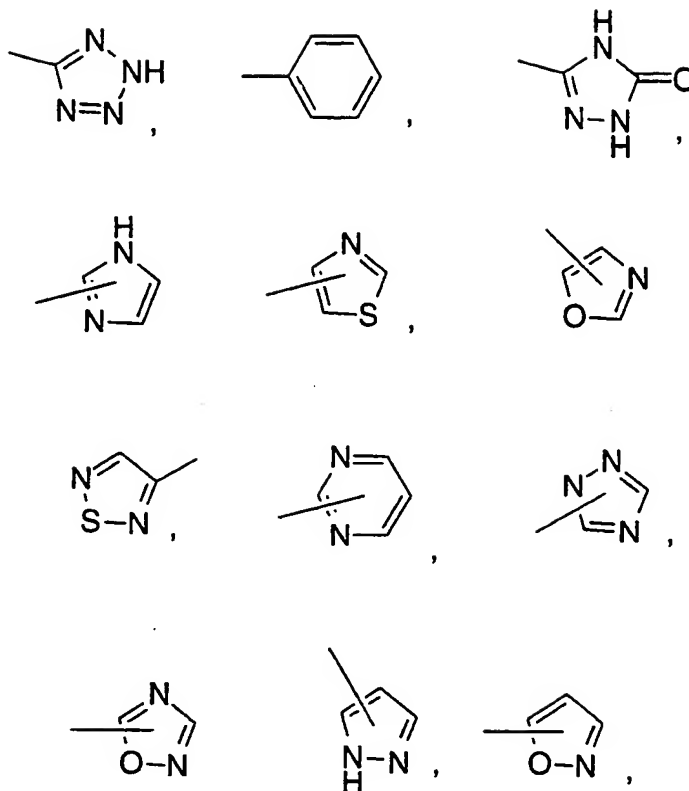
R₄ and R₅ are independently selected from the group consisting of:



R₆ is hydrogen, C₁-C₆ alkyl or (CH₂)_varyl wherein the alkyl and (CH₂)_v groups may be optionally substituted by halogen, OR₂,
 25 N(R₂)(R₂), C₃-C₆ cycloalkyl, 1H-tetrazol-5-yl, C(O)OR₂, C(O)N(R₂)(R₂), SO₂N(R₂)(R₂) or N(R₂)C(O)N(R₂)(R₂), wherein aryl is selected from the following aromatic groups and their regioisomers:

30

- 34 -



where the aromatic groups are optionally substituted with C₁-C₂ alkyl,
 20 -N(R₂)(R₂), or hydroxy;

m is 0, 1, or 2;

r is 0, 1, 2, or 3;

q is 0 or 1;

25 t is 0 or 1;

v is 0 or 1;

and pharmaceutically acceptable salts and individual diastereomers
 thereof.

30 Representative of the still more preferred compounds
 within this second embodiment include the following:

- 35 -

5

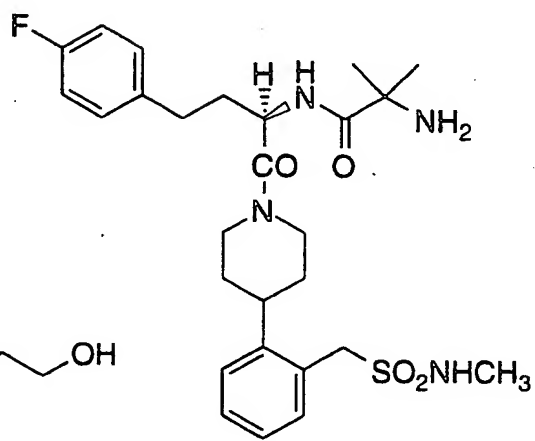
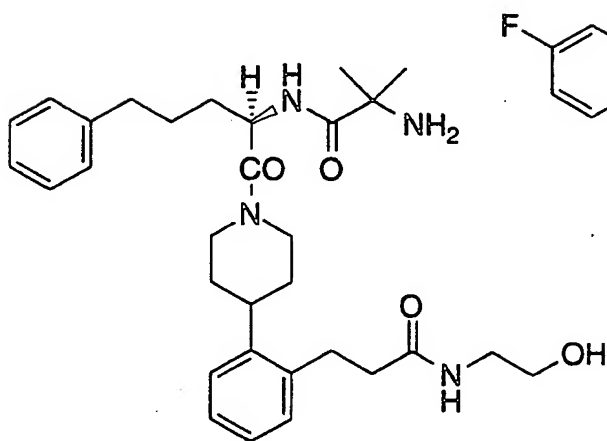
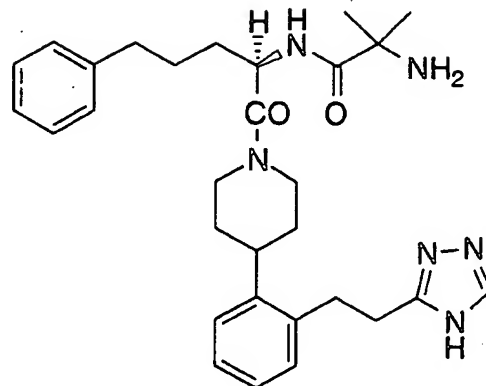
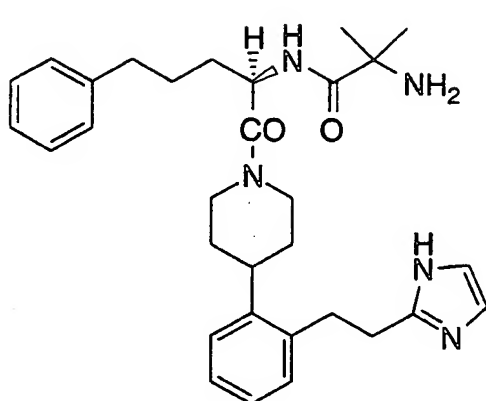
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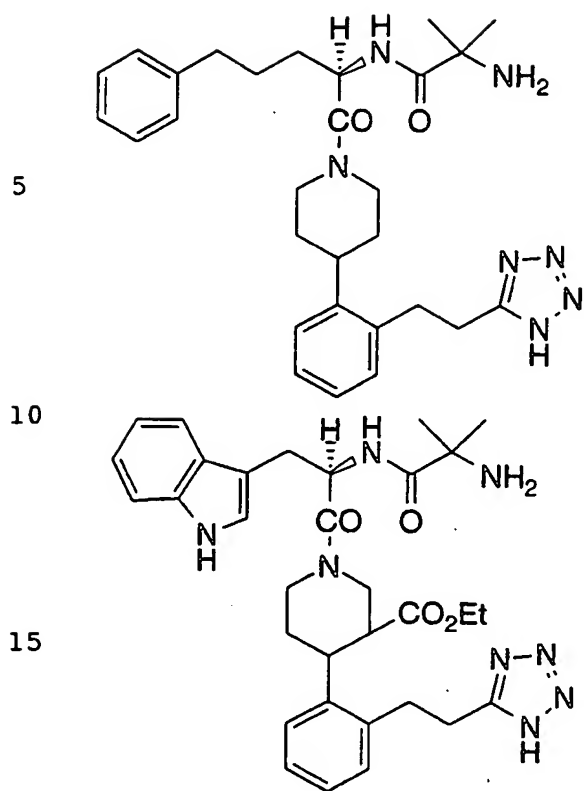
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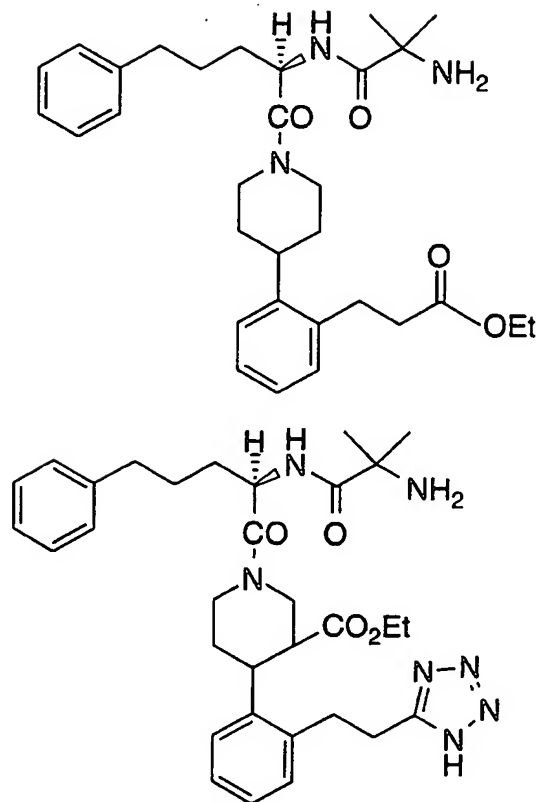


- 36 -



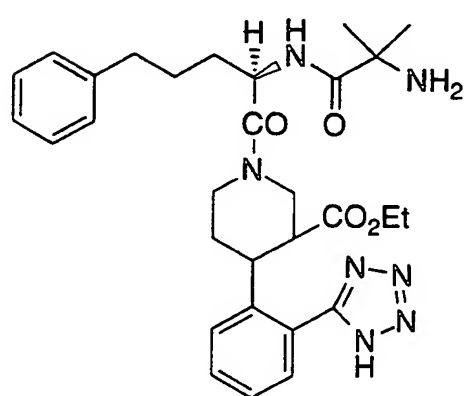
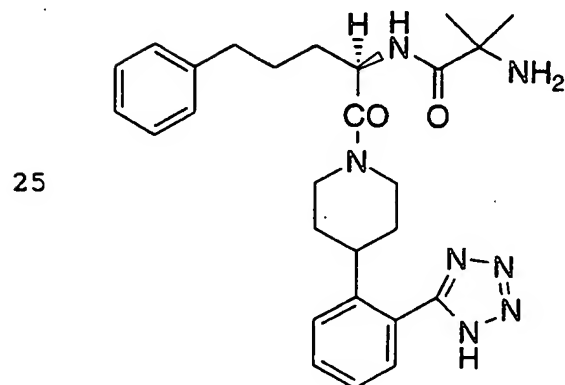
cis d₁, cis d₂, trans d₁, trans d₂

20



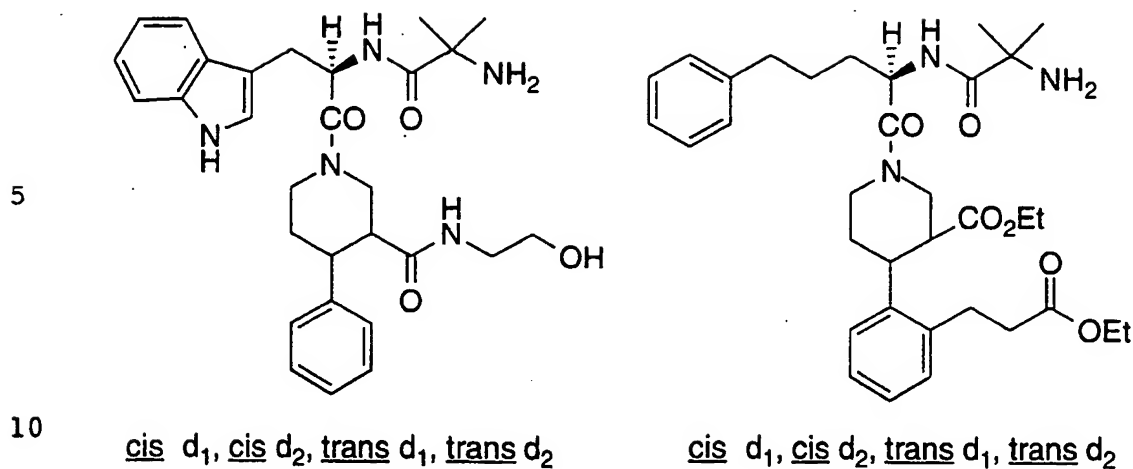
cis d₁, cis d₂, trans d₁, trans d₂

25



cis d₁, cis d₂, trans d₁, trans d₂

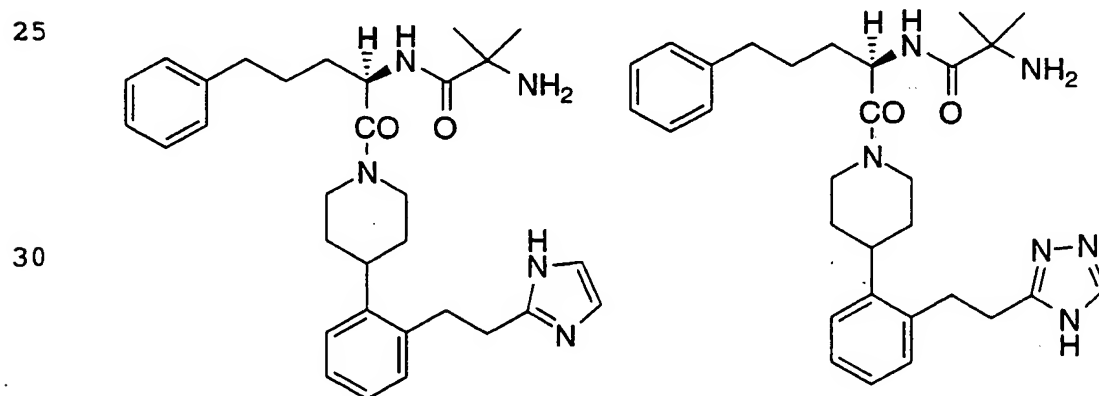
- 37 -



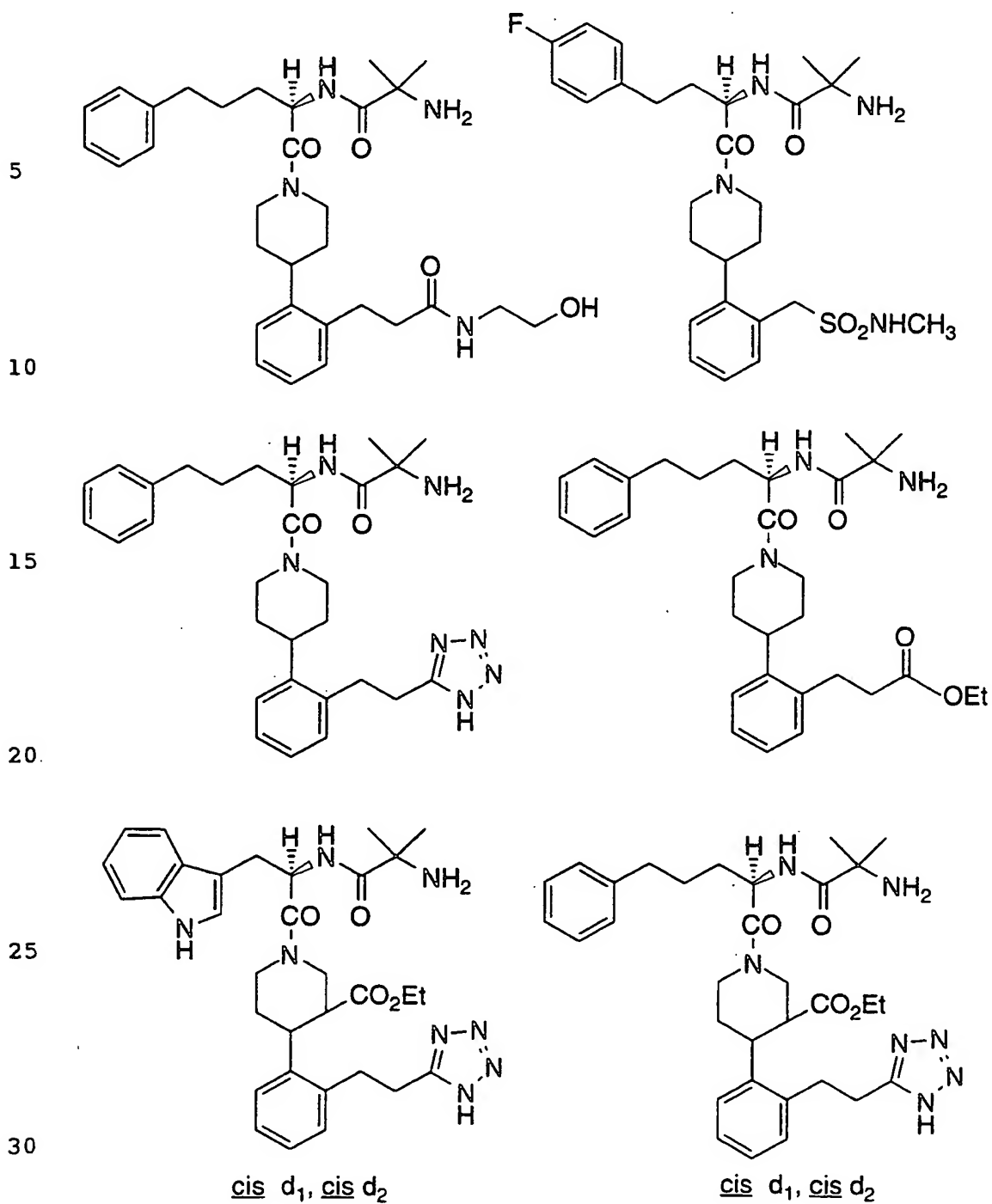
and pharmaceutically acceptable salts and individual diastereomers thereof where not otherwise specified.

15 All of the still more preferred compounds shown above have at least one asymmetric center. Additional asymmetric centers may be present on the molecule depending upon the nature of the substituents on the piperidine ring. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers, racemic mixtures or
20 diastereomeric mixtures thereof, be included within the ambit of the present invention.

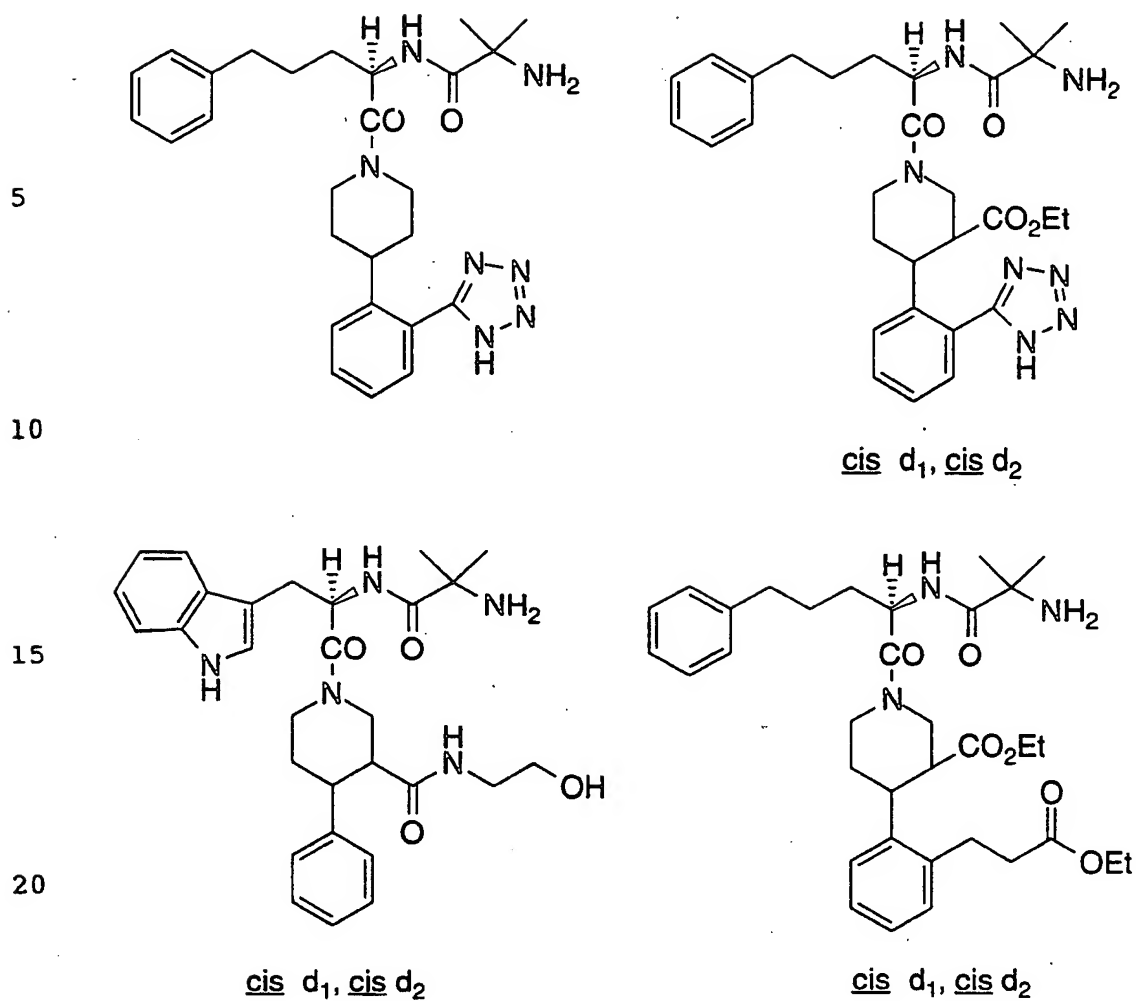
The most preferred compounds within this second embodiment include the following:



- 38 -



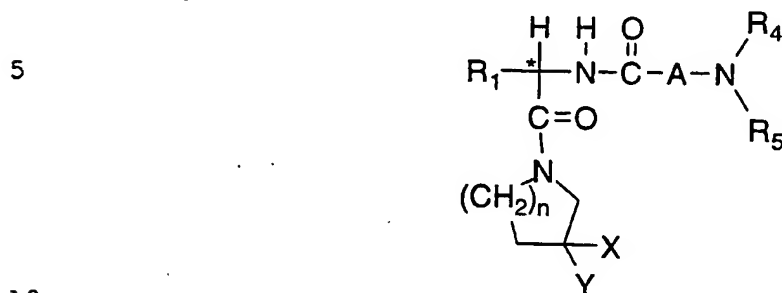
- 39 -



and their pharmaceutically acceptable salts and individual diastereomers thereof where not otherwise specified.

- 40 -

A third embodiment of the present invention is directed to the compounds of the structural formula CI:



Formula CI

wherein:

R₁ is selected from the group consisting of:

- 15 C₁-C₁₀ alkyl, aryl, aryl(C₁-C₆ alkyl), (C₃-C₇ cycloalkyl)(C₁-C₆ alkyl)-, (C₁-C₅ alkyl)-K-(C₁-C₅ alkyl)-, aryl(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, and (C₃-C₇ cycloalkyl)(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, where K is O, S(O)_m, N(R₂)C(O), C(O)N(R₂), OC(O), C(O)O, -CR₂=CR₂-, or -C≡C-, where aryl is selected from: phenyl, naphthyl, indolyl, azaindole,
- 20 pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl, and R₂ and alkyl may be further substituted by 1 to 9 halogen, S(O)_mR_{2a}, 1 to 3 of OR_{2a} or C(O)OR_{2a}, and aryl may be further substituted by 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of OR₂, methylenedioxy, -S(O)_mR₂, 1 to 2 of -CF₃, -OCF₃, nitro, -N(R₂)C(O)(R₂), -C(O)OR₂,
- 25 -C(O)N(R₂)(R₂), -1H-tetrazol-5-yl, -SO₂N(R₂)(R₂), -N(R₂)SO₂ phenyl, or -N(R₂)SO₂R₂;

R₂ is selected from: hydrogen, C₁-C₆ alkyl, and C₃-C₇ cycloalkyl, and where two C₁-C₆ alkyl groups are present on one atom, they may be

30 optionally joined to form a C₃-C₈ cyclic ring, optionally including oxygen, sulfur or NR_{3a}, where R_{3a} is hydrogen, or C₁-C₆ alkyl, optionally substituted by hydroxyl;

R_{2a} is hydrogen, or C₁-C₆ alkyl optionally substituted by hydroxyl;

- 41 -

X is selected from: hydrogen, $-\text{C}\equiv\text{N}$, $-(\text{CH}_2)_q\text{N}(\text{R}_2)\text{C}(\text{O})\text{R}_2$,
 $-(\text{CH}_2)_q\text{N}(\text{R}_2)\text{C}(\text{O})(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_q\text{N}(\text{R}_2)\text{SO}_2(\text{CH}_2)_t\text{aryl}$,
 $-(\text{CH}_2)_q\text{N}(\text{R}_2)\text{SO}_2\text{R}_2$, $-(\text{CH}_2)_q\text{N}(\text{R}_2)\text{C}(\text{O})\text{N}(\text{R}_2)(\text{CH}_2)_t\text{aryl}$,
 $-(\text{CH}_2)_q\text{N}(\text{R}_2)\text{C}(\text{O})\text{N}(\text{R}_2)(\text{R}_2)$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{N}(\text{R}_2)(\text{R}_2)$,
5 $-(\text{CH}_2)_q\text{C}(\text{O})\text{N}(\text{R}_2)(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}_2$,
 $-(\text{CH}_2)_q\text{C}(\text{O})\text{O}(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_q\text{OR}_2$, $-(\text{CH}_2)_q\text{OC}(\text{O})\text{R}_2$,
 $-(\text{CH}_2)_q\text{OC}(\text{O})(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_q\text{OC}(\text{O})\text{N}(\text{R}_2)(\text{CH}_2)_t\text{aryl}$,
 $-(\text{CH}_2)_q\text{OC}(\text{O})\text{N}(\text{R}_2)(\text{R}_2)$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{R}_2$, $-(\text{CH}_2)_q\text{C}(\text{O})(\text{CH}_2)_t\text{aryl}$,
 $-(\text{CH}_2)_q\text{N}(\text{R}_2)\text{C}(\text{O})\text{OR}_2$, $-(\text{CH}_2)_q\text{N}(\text{R}_2)\text{SO}_2\text{N}(\text{R}_2)(\text{R}_2)$,
10 $-(\text{CH}_2)_q\text{S}(\text{O})_m\text{R}_2$, and $-(\text{CH}_2)_q\text{S}(\text{O})_m(\text{CH}_2)_t\text{aryl}$, where an R_2 , $(\text{CH}_2)_q$
and $(\text{CH}_2)_t$ group may be optionally substituted by 1 to 2 C_1 - C_4 alkyl,
hydroxyl, C_1 - C_4 lower alkoxy, carboxyl, CONH_2 , $\text{S}(\text{O})_m\text{CH}_3$,
carboxylate C_1 - C_4 alkyl esters, or 1H-tetrazol-5-yl, and aryl is phenyl,
naphthyl, pyridyl, thiazolyl, or 1H-tetrazol-5-yl groups which may be
15 optionally substituted by 1 to 3 halogen, 1 to 3 $-\text{OR}_2$, $-\text{CON}(\text{R}_2)(\text{R}_2)$,
 $-\text{C}(\text{O})\text{OR}_2$, 1 to 3 C_1 - C_4 alkyl, $-\text{S}(\text{O})_m\text{R}_2$, or 1H-tetrazol-5-yl;

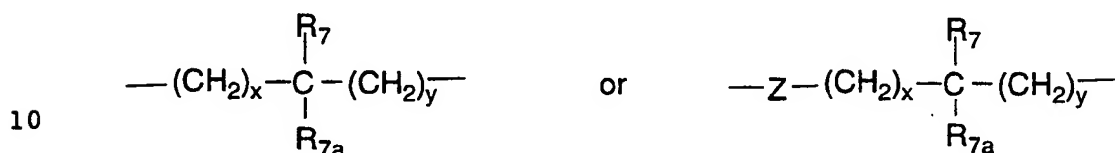
Y is selected from: hydrogen, C_1 - C_{10} alkyl, $-(\text{CH}_2)_t\text{aryl}$,
 $-(\text{CH}_2)_q(\text{C}_3\text{-C}_7\text{ cycloalkyl})$, $-(\text{CH}_2)_q\text{-K-(C}_1\text{-C}_6\text{ alkyl)}$,
20 $-(\text{CH}_2)_q\text{-K-(CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_q\text{-K-(CH}_2)_t(\text{C}_3\text{-C}_7\text{ cycloalkyl})$
containing O, NR_2 , S), and $-(\text{CH}_2)_q\text{-K-(CH}_2)_t(\text{C}_3\text{-C}_7\text{ cycloalkyl})$, where
K is O, $\text{S}(\text{O})_m$, $\text{C}(\text{O})\text{NR}_2$, $\text{CH}=\text{CH}$, $\text{C}\equiv\text{C}$, $\text{N}(\text{R}_2)\text{C}(\text{O})$, $\text{C}(\text{O})\text{NR}_2$, $\text{C}(\text{O})\text{O}$,
or $\text{OC}(\text{O})$, and where the alkyl, R_2 , $(\text{CH}_2)_q$ and $(\text{CH}_2)_t$ groups may be
optionally substituted by C_1 - C_4 alkyl, hydroxyl, C_1 - C_4 lower alkoxy,
25 carboxyl, $-\text{CONH}_2$ or carboxylate C_1 - C_4 alkyl esters, and aryl is phenyl,
naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl,
pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiophenyl,
quinolinyl, pyrazinyl, or isothiazolyl which is optionally substituted by 1
to 3 halogen, 1 to 3 $-\text{OR}_2$, $-\text{C}(\text{O})\text{OR}_2$, $-\text{C}(\text{O})\text{N}(\text{R}_2)(\text{R}_2)$, nitro, cyano,
30 benzyl, 1 to 3 C_1 - C_4 alkyl, $-\text{S}(\text{O})_m\text{R}_2$, or 1H-tetrazol-5-yl, with the
proviso that if X is hydrogen, Y is other than hydrogen;

R_4 and R_5 are independently hydrogen, C_1 - C_6 alkyl, or substituted C_1 - C_6 alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxy, 1 to 3

- 42 -

C₁-C₁₀ alkanoyloxy, 1 to 3 C₁-C₆ alkoxy, phenyl, phenyloxy, 2-furyl, C₁-C₆ alkoxy carbonyl, S(O)_m(C₁-C₆ alkyl), or R₄ and R₅ may be taken together to form -(CH₂)_d-L_a(CH₂)_e- where L_a is -C(R₂)₂-, O, S(O)_m or N(R₂), d and e are independently 1 to 3 and R₂ is as defined above;

A is:



where x and y are independently 0, 1, 2 or 3;

Z is N-R_{6a} or O, where R_{6a} is hydrogen or C₁-C₆ alkyl;

R₇ and R_{7a} are independently hydrogen, C₁-C₆ alkyl, trifluoromethyl, phenyl, or substituted C₁-C₆ alkyl where the substituents are imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)_mR₂, C(O)OR₂, C₃-C₇ cycloalkyl, N(R₂)(R₂), C(O)N(R₂)(R₂), or R₇ and R_{7a} may independently be joined to one or both of R₄ and R₅ groups to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R₇ or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms, or R₇ and R_{7a} can be joined to one another to form C₃-C₇ cycloalkyl;

m is 0, 1, or 2;

n is 1, 2, or 3;

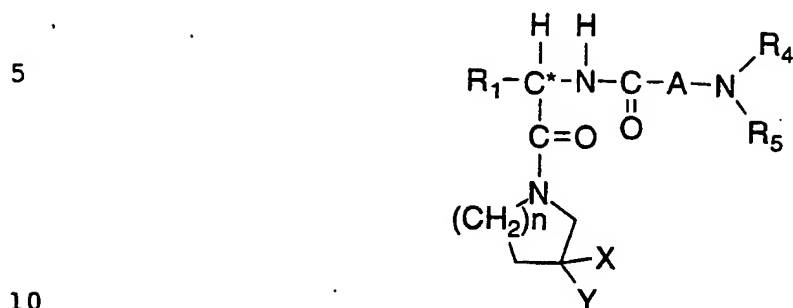
q is 0, 1, 2, 3, or 4;

t is 0, 1, 2, or 3;

and pharmaceutically acceptable salts and individual diastereomers thereof.

- 43 -

Preferred compounds within this third embodiment include those of Formula CIa:



Formula CIa

wherein:

R₁ is selected from the group consisting of:

- 15 C₁-C₁₀ alkyl, aryl (C₁-C₄ alkyl)-, C₃-C₆ cycloalkyl (C₁-C₄ alkyl)-, (C₁-C₄ alkyl)-K-(C₁-C₂ alkyl)-, aryl (C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-, and (C₃-C₇ cycloalkyl)(C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-, where K is O, S(O)_m, OC(O), or C(O)O, and the alkyl groups may be further substituted by 1 to 7 halogen, S(O)_mR₂, 1 to 3 OR₂ or C(O)OR₂, and
- 20 aryl is phenyl, naphthyl, indolyl, pyridyl, benzimidazolyl, azaindoleyl, benzothienyl or benzofuranyl which may be further substituted by 1-2 C₁-C₄ alkyl, 1 to 2 halogen, 1 to 2 -OR₂, -S(O)_mR₂, or -C(O)OR₂;

- R₂ is hydrogen, C₁-C₆ alkyl, or C₃-C₇ cycloalkyl, and where two C₁-C₆ alkyl groups are present on one atom they may be optionally joined to form a C₄-C₇ cyclic ring optionally including oxygen, sulfur or NR_{3a};
- 25

R_{3a} is hydrogen, or C₁-C₄ alkyl;

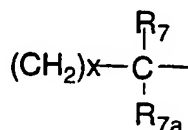
- 30 X is selected from: hydrogen, -(CH₂)_qN(R₂)C(O)R₂, -(CH₂)_qN(R₂)C(O)(CH₂)_taryl, -(CH₂)_qN(R₂)C(O)OR₂, -(CH₂)_qN(R₂)SO₂(CH₂)_taryl, -(CH₂)_qN(R₂)SO₂R₂, -(CH₂)_qN(R₂)C(O)N(R₂)(CH₂)_taryl, -(CH₂)_qN(R₂)C(O)N(R₂)(R₂), -(CH₂)_qC(O)N(R₂)(R₂), -(CH₂)_qC(O)N(R₂)(CH₂)_taryl, -(CH₂)_qC(O)OR₂, -(CH₂)_qC(O)O(CH₂)_taryl, -(CH₂)_qOC(O)R₂,

- 44 -

$-(CH_2)_qOC(O)(CH_2)_taryl$, $-(CH_2)_qS(O)_mR_2$, and
 $-(CH_2)_qS(O)_m(CH_2)_taryl$, where an R_2 group may be optionally
 substituted by hydroxyl, carboxyl, $CONH_2$, $S(O)_mCH_3$, carboxylate C_1 -
 C_4 alkyl esters, or tetrazole, and aryl is phenyl, naphthyl, pyridyl or 1-H-
 5 tetrazolyl which may be optionally substituted by 1 to 2 halogen, 1 to 2
 $-OR_2$, $-CONH_2$, $-C(O)OR_2$, 1 to 3 C_1 - C_4 alkyl, $-S(O)_mR_2$, or 1H-
 tetrazole-5-yl;

Y is selected from: hydrogen, C_1 - C_8 alkyl, $(CH_2)_taryl$, $-(CH_2)_q(C_5$ - C_6
 10 cycloalkyl), $-(CH_2)_qK-(C_1$ - C_6 alkyl), $-(CH_2)_qK-(CH_2)_taryl$,
 $-(CH_2)_qK-(CH_2)_t(C_3$ - C_7 cycloalkyl containing O, NR_2 , or S), and
 $-(CH_2)_qK-(CH_2)_t(C_5$ - C_6 cycloalkyl), where K is O or $S(O)_m$ and
 where the alkyl groups may be optionally substituted by hydroxyl,
 carboxyl, $CONH_2$, carboxylate C_1 - C_4 alkyl esters or 1H-tetrazole-5-yl
 15 and aryl is phenyl, naphthyl, pyridyl, 1-H-tetrazolyl, thiazolyl,
 imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl,
 isoxazolyl, or thiophenyl which is optionally substituted by 1 to 3
 halogen, 1 to 3 $-OR_2$, $-C(O)OR_2$, $-C(O)N(R_2)(R_2)$, cyano, 1 to 2 C_1 - C_4
 20 alkyl, benzyl, $-S(O)_mR_2$, or 1H-tetrazol-5-yl, with the proviso that if X is
 hydrogen, Y is other than hydrogen;

R_4 and R_5 are independently hydrogen, C_1 - C_6 alkyl, or substituted C_1 -
 C_6 alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxyl,
 $S(O)_m(C_1$ - C_6 alkyl) or phenyl;
 25 A is:



30 where x is 0, or 1;

R_7 and R_{7a} are independently hydrogen C_1 - C_6 alkyl, trifluoromethyl,
 phenyl, substituted C_1 - C_6 alkyl where the substituents are imidazolyl,
 phenyl, indolyl, p-hydroxyphenyl, OR_2 , $S(O)_mR_2$, $C(O)OR_2$, C_5 - C_7

- 45 -

cycloalkyl, -N(R₂)(R₂), -C(O)N(R₂)(R₂); or R₇ and R_{7a} can independently be joined to one of R₄ or R₅ to form alkylene bridges between the terminal nitrogen and the alkyl portion of R₇ or R_{7a} groups to form 5 or 6 membered rings; or R₇ and R_{7a} can be joined to one
 5 another to form a C₃ cycloalkyl;

n is 2;

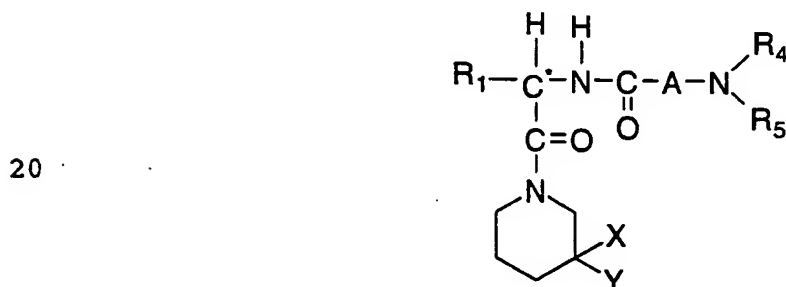
m is 0, 1, or 2;

q is 0, 1, 2, or 3;

10 t is 0, 1, 2, or 3;

and pharmaceutically acceptable salts and individual diastereomers thereof.

15 More preferred compounds within this third embodiment include those of Formula CIb:



Formula CIb

25

wherein:

R₁ is selected from the group consisting of: C₁-C₁₀ alkyl, aryl (C₁-C₃ alkyl)-, (C₃-C₇ cycloalkyl)(C₁-C₃ alkyl)-, and aryl (C₀-C₁ alkyl)-K-(C₁-C₂ alkyl)-, where K is O or S(O)_m and the aryl
 30 is phenyl, pyridyl, naphthyl, indolyl, azaindolyl, or benzimidazolyl which is optionally substituted by 1-2 C₁-C₄ alkyl, 1 to 2 halogen, 1 to 2 OR₂, S(O)_m R₂, or C(O)OR₂;

- 46 -

R₂ is hydrogen, C₁-C₆ alkyl, or C₃-C₇ cycloalkyl, and where two C₁-C₆ alkyl groups are present on one atom they may be optionally joined to form a C₅-C₇ cyclic ring optionally including oxygen, sulfur or NR_{3a};

5 R_{3a} is hydrogen, or C₁-C₄ alkyl;

X is selected from: hydrogen, -(CH₂)_qN(R₂)C(O)R₂,
 -(CH₂)_qN(R₂)C(O)(CH₂)_taryl, -(CH₂)_qN(R₂)SO₂(CH₂)_taryl, -(CH₂)_q
 N(R₂)SO₂R₂, -(CH₂)_qN(R₂)C(O)N(R₂)(CH₂)_taryl,
 10 -(CH₂)_qN(R₂)C(O)N(R₂)(R₂), -(CH₂)_qC(O)N(R₂)(R₂),
 -(CH₂)_qN(R₂)C(O)OR₂, -(CH₂)_qC(O)N(R₂)(CH₂)_taryl,
 -(CH₂)_qC(O)OR₂, -(CH₂)_qC(O)O(CH₂)_taryl, -(CH₂)_qOC(O)R₂,
 -(CH₂)_qOC(O)(CH₂)_taryl, -(CH₂)_qS(O)_mR₂, and
 -(CH₂)_qS(O)_m(CH₂)_taryl, where an R₂ group may be optionally
 15 substituted by hydroxyl, carboxyl, -CONH₂, -S(O)_mCH₃, carboxylate
 C₁-C₄ alkyl esters or tetrazole and aryl is phenyl, naphthyl or pyridyl
 which may be further substituted by 1-2 halogen, 1 to 2 OR₂, C(O)OR₂,
 1 to 3 C₁-C₄ alkyl, S(O)_mR₂, or 1H-tetrazole-5-yl;

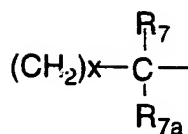
20 Y is selected from: hydrogen, C₁-C₈ alkyl, (CH₂)_taryl, -(CH₂)_q C₅-C₇
 cycloalkyl, -(CH₂)_q-K-(C₁-C₆ alkyl), -(CH₂)_q-K-(CH₂)_taryl, and
 -(CH₂)_q-K-(CH₂)_t (C₅-C₆ cycloalkyl), where K is S(O)_m and where the
 alkyl groups may be optionally substituted by hydroxyl, carboxyl,
 CONH₂, carboxylate C₁-C₄ alkyl esters or 1H-tetrazole-5-yl and aryl is
 25 phenyl, naphthyl, pyridyl, thiazolyl, thiophenyl, pyrazolyl, oxazolyl,
 isoxazolyl or imidazolyl which may be optionally substituted by 1 to 2
 halogen, 1 to 2 OR₂, 1 to 2 -N(R₂)(R₂), CO(OR₂), 1 to 2 C₁-C₄ alkyl,
 S(O)_mR₂, or 1H-tetrazol-5-yl, with the proviso that if X is hydrogen, Y
 is other than hydrogen;

30

R₄ and R₅ are independently hydrogen, C₁-C₄ alkyl, or substituted C₁-
 C₃ alkyl where the substituents may be 1 to 2 hydroxyl;

A is

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5 where x is 0, or 1;

R₇ and R_{7a} are independently hydrogen, C₁-C₆ alkyl, phenyl, substituted C₁-C₆ alky wherein the substituent is imidixolyl, phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)_mR₂, or R₇ and R_{7a} may be joined to one
 10 another to form a C₃ cycloalkyl;

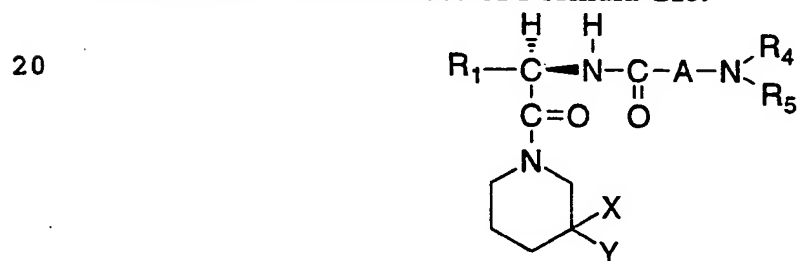
m is 0, 1, or 2;

q is 0, 1, 2, or 3;

t is 0, 1, 2, or 3;

15 and pharmaceutically acceptable salts and individual diastereomers thereof.

Still more preferred compounds within this third embodiment include those of Formula CIc:



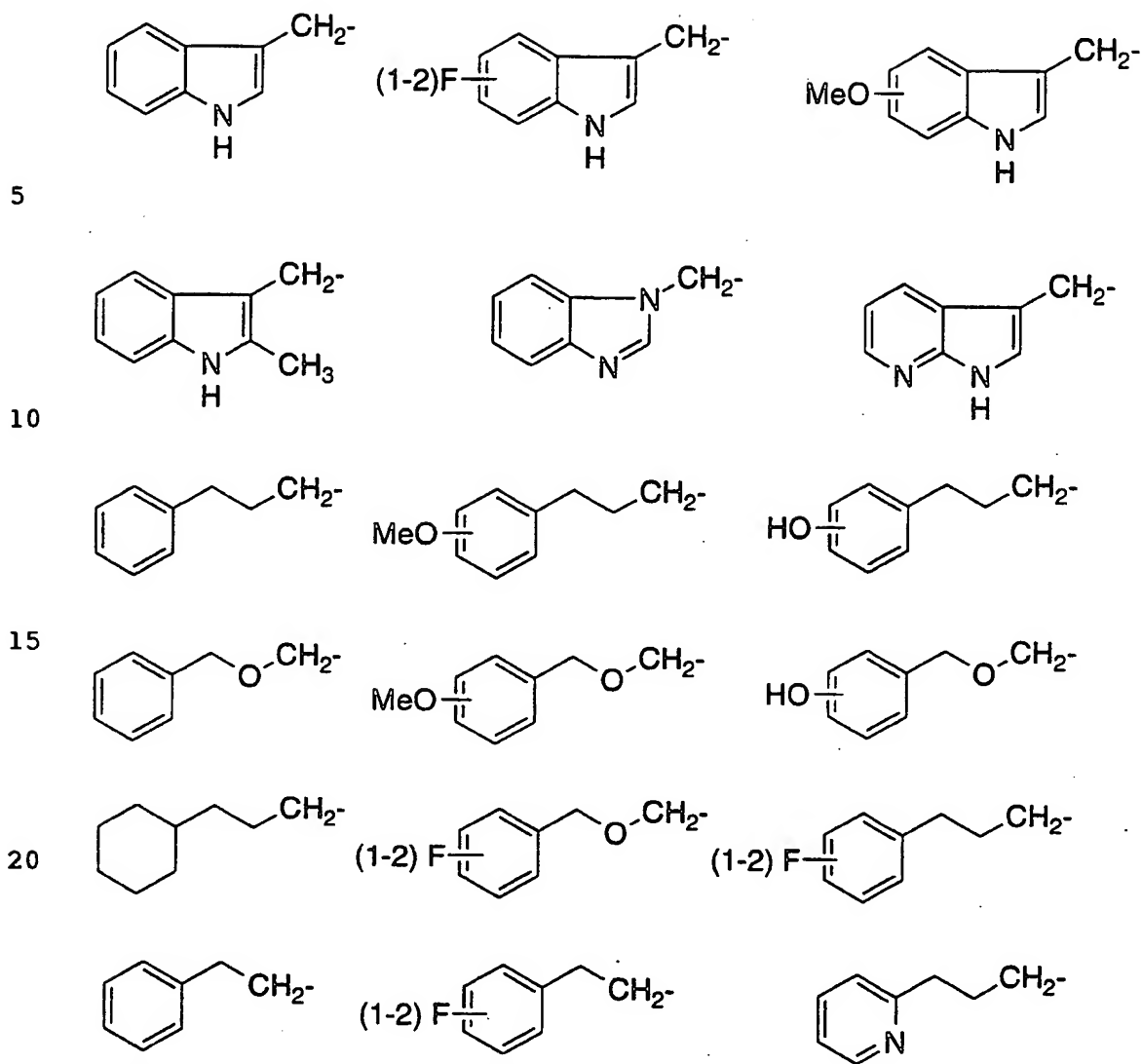
25 Formula CIc

wherein:

R₁ is selected from the group consisting of:

30

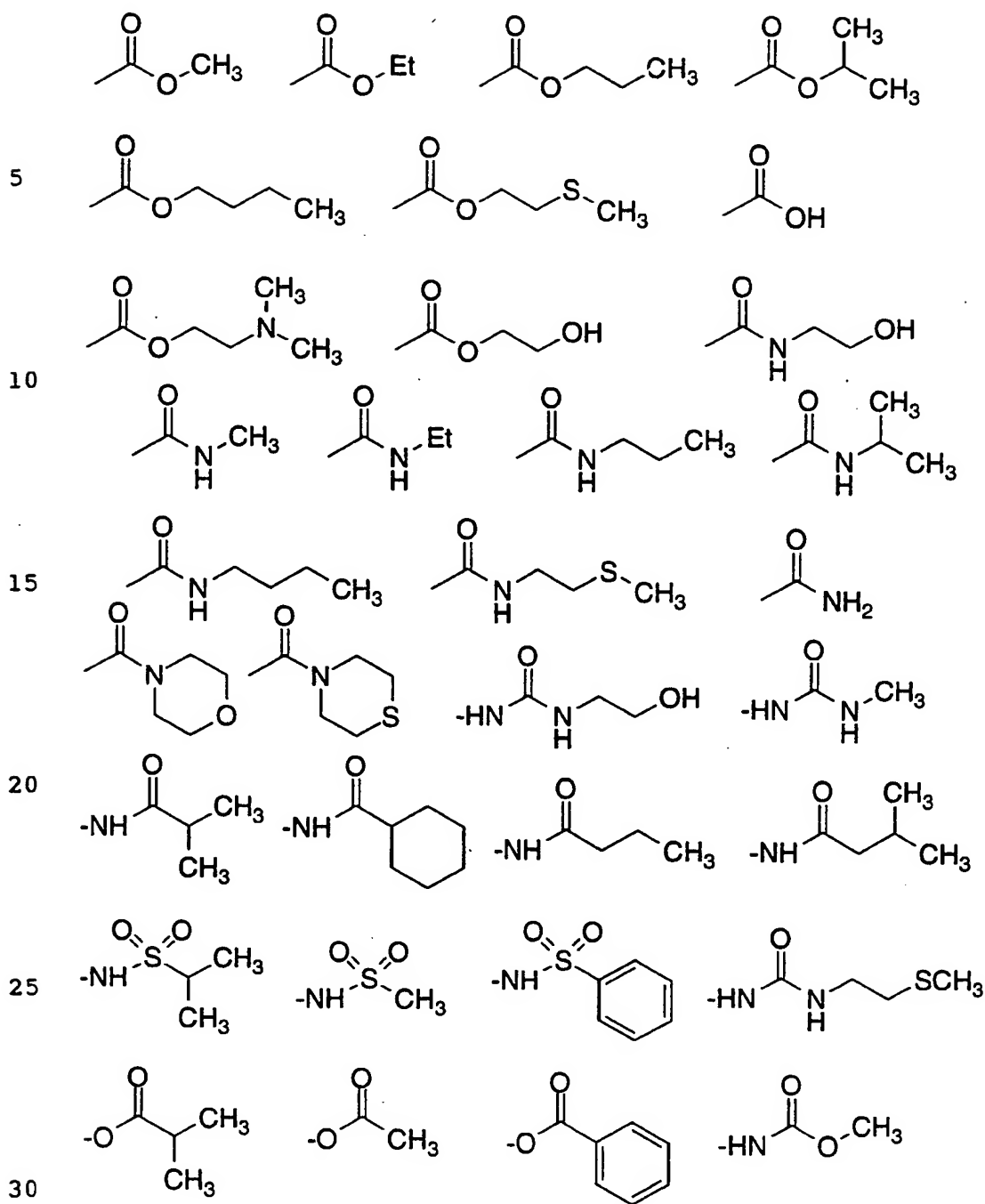
- 48 -



X is selected from the group consisting of: hydrogen,

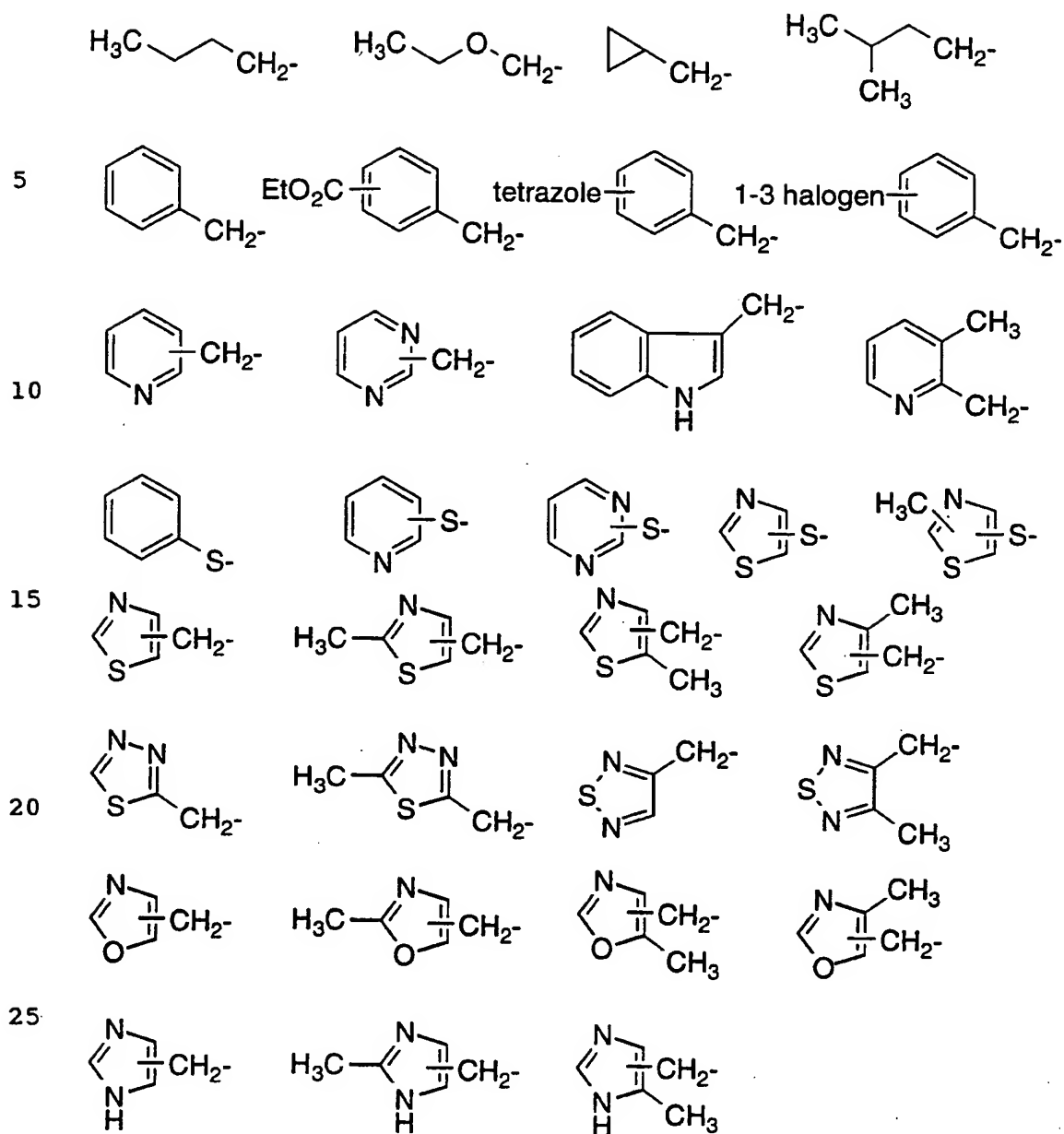
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- 49 -



Y is selected from the group consisting of: hydrogen,

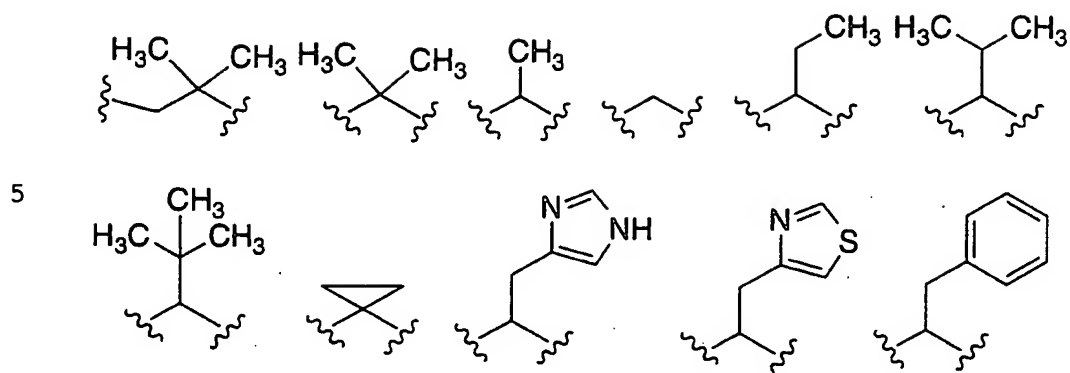
- 50 -



or their regioisomers whereof where not specified, with the proviso that if X is hydrogen, Y is other than hydrogen;

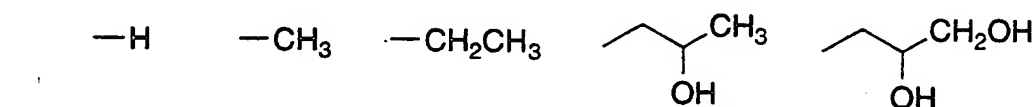
A is selected from the group consisting of:

- 51 -



10

R₄ and R₅ are independently selected from the group consisting of:

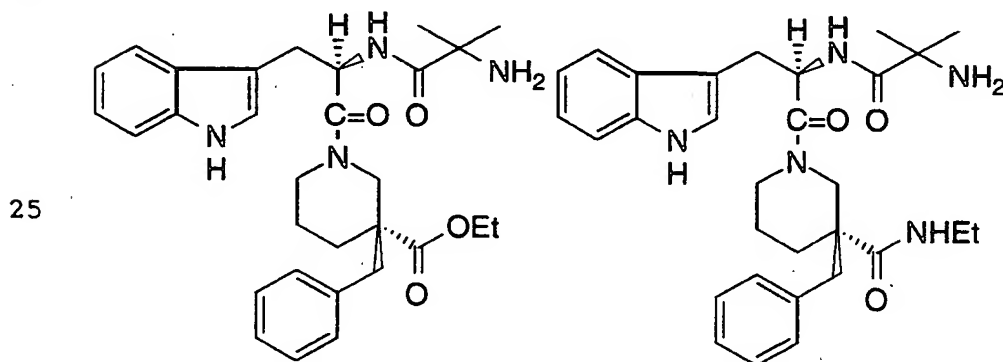


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and pharmaceutically acceptable salts and individual diastereomers thereof.

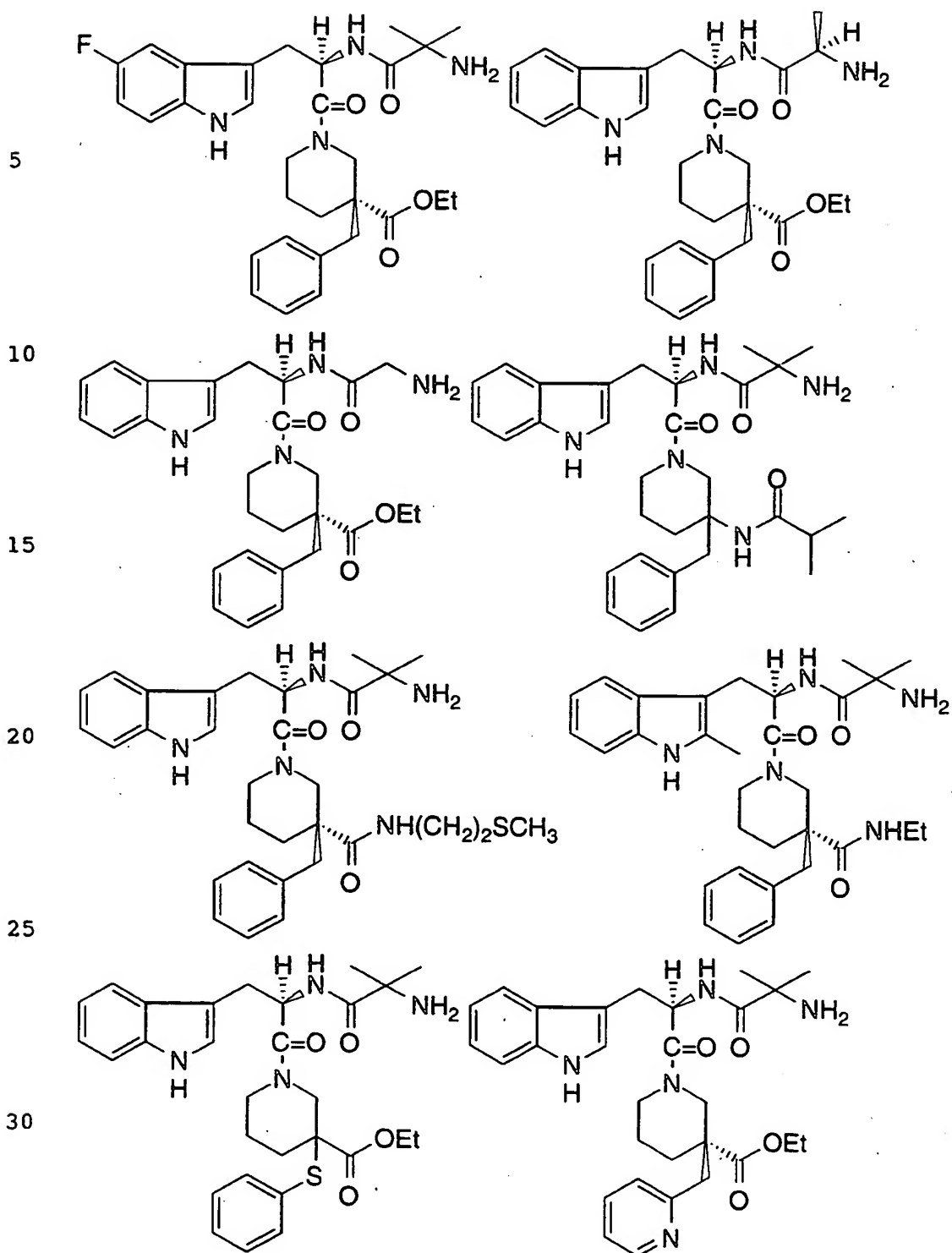
The most preferred compounds within this third embodiment include the following:

20

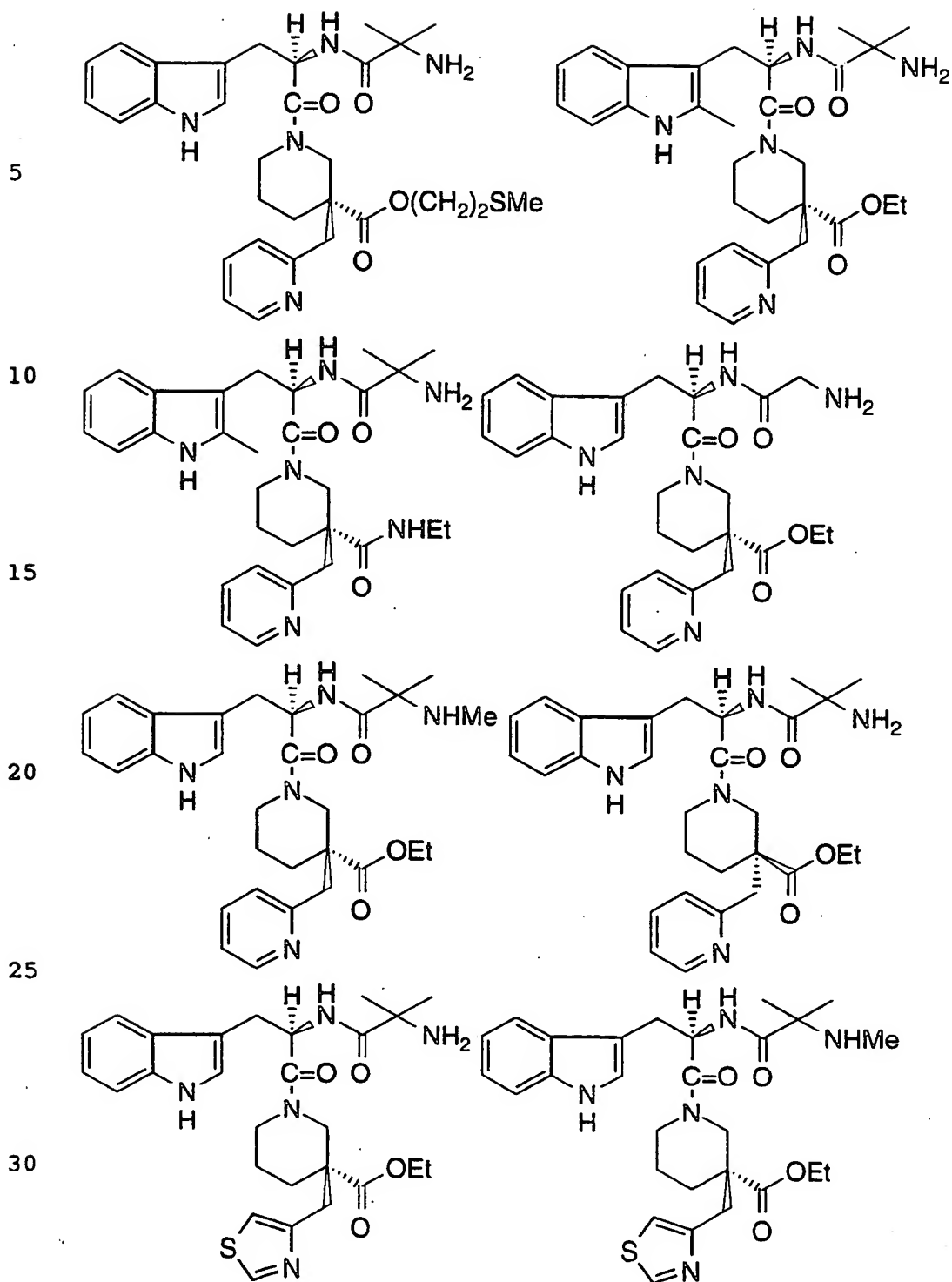


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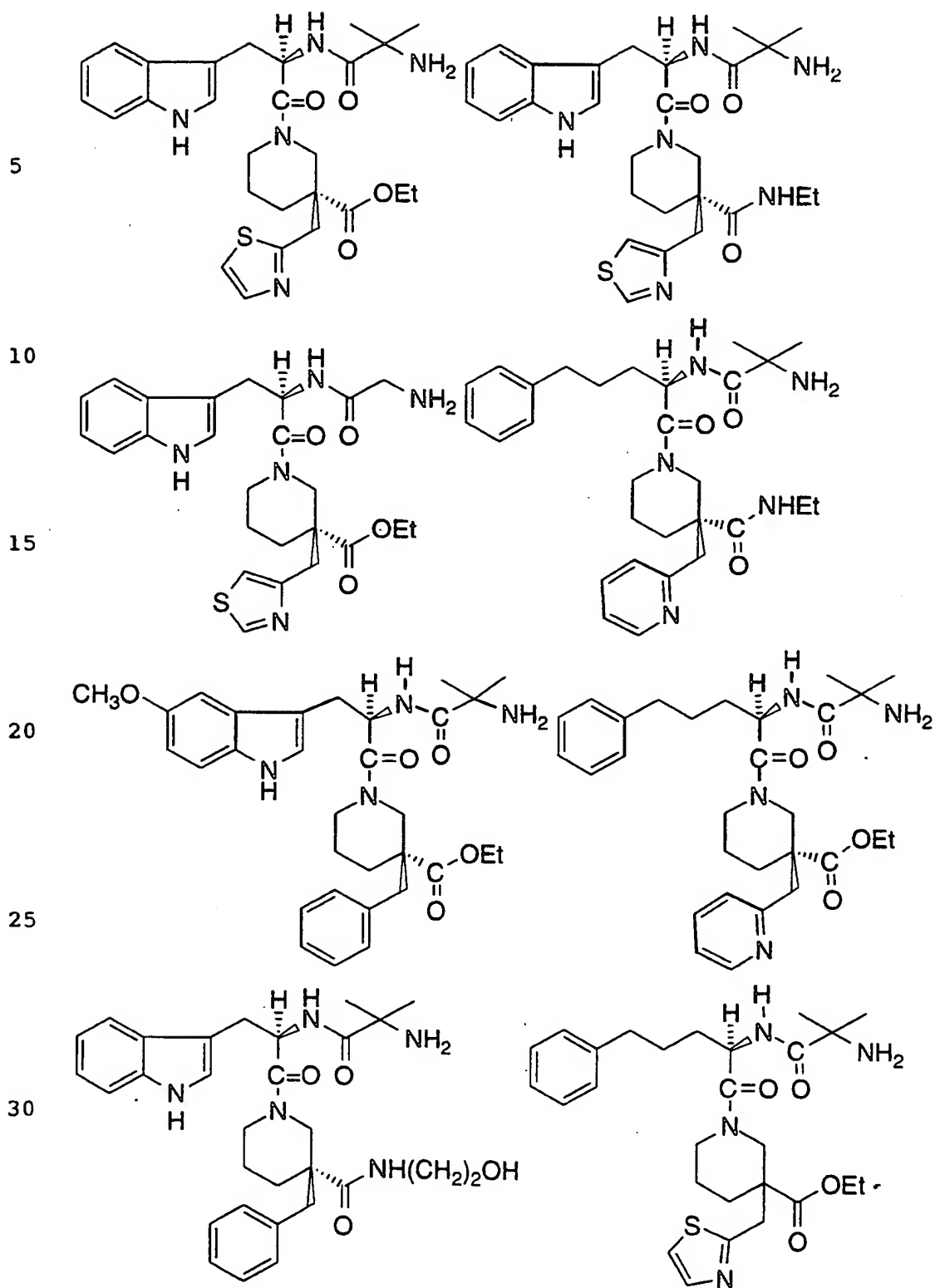
- 52 -



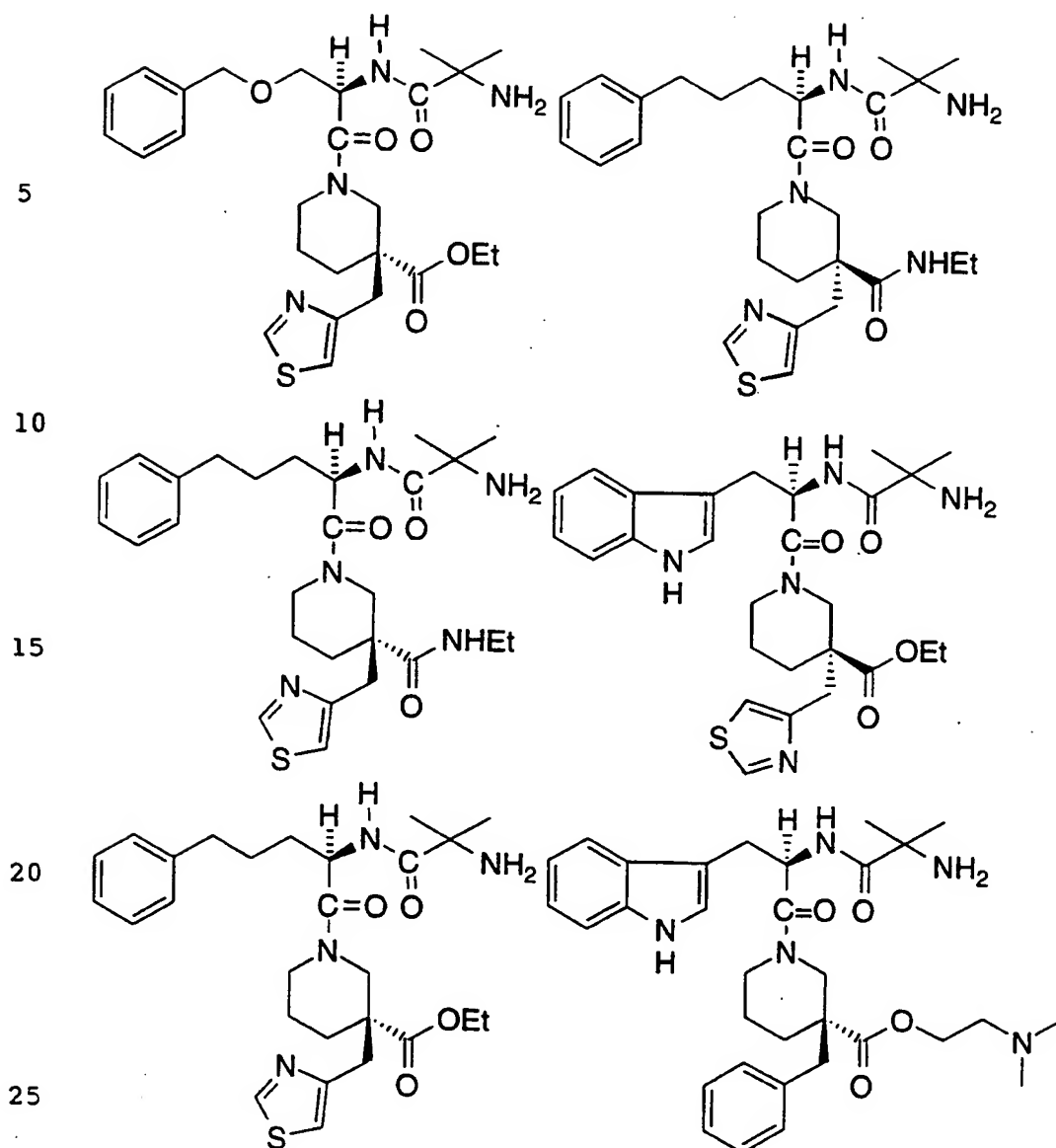
- 53 -



- 54 -



- 55 -



and their pharmaceutically acceptable salts and individual diastereomers thereof where not otherwise specified.

30 Throughout the instant application, the following abbreviations are used with the following meanings:

| | |
|-----|--|
| BOC | t-butyloxycarbonyl |
| BOP | Benzotriazol-1-yloxy tris(dimethylamino)-phosphonium hexafluorophosphate |
| CBZ | Benzylloxycarbonyl |

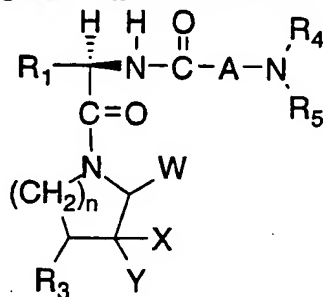
- 56 -

| | | |
|----|---------|--|
| | DIBAL-H | diisobutylaluminum hydride |
| | DMF | N,N-dimethylformamide |
| | EDC | 1-(3-dimethylaminopropyl)-3-ethylcarbodi- imide hydrochloride |
| 5 | FAB-MS | Fast atom bombardment-mass spectroscopy |
| | GHRP | Growth hormone releasing peptide |
| | HOBT | Hydroxybenztriazole |
| | LAH | Lithium aluminum hydride |
| | HPLC | High pressure liquid chromatography |
| 10 | MHz | Megahertz |
| | MPLC | Medium pressure liquid chromatography |
| | NMM | N-Methylmorpholine |
| | NMR | Nuclear Magnetic Resonance |
| | TFA | Trifluoroacetic acid |
| 15 | THF | Tetrahydrofuran |
| | TLC | Thin layer chromatography |
| | TMS | Tetramethylsilane |

20 The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in the structural Formula I above. Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, 25 pure or partially purified optical isomers, racemic mixtures or diastereomeric mixtures thereof, be included within the ambit of the instant invention. In the case of the asymmetric center represented by the asterisk in Formula I, it has been found that the absolute stereochemistry of the more active and thus more preferred isomer is 30 as shown in Formula II. An equivalent representation places R₁ and the N-substituent in the plane of the structure with the C=O group above. The special configuration of the asymmetric center corresponds to that in a D-amino acid. In most cases this is also

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designated an R-configuration although this will vary according to the value of R₁ used in making R- or S- stereochemical assignments.



Formula II

The W group may also be present in either R- or S- configurations. Both afford active growth hormone secretagogues although, in general, the R- configuration is more active. In addition, the W group may be cis- or trans- in respect to substituents X, Y or R₃. In the case of the asymmetric center which bears the X and Y groups, in most cases, both the R- and S- configurations are consistent with useful levels of growth hormone secretagogue activity. In addition, configurations of many of the most preferred compounds of this invention are indicated. The W, X and Y groups may also be cis- or trans- to the R₃ substituent. In some of the most preferred compounds a cis- or trans- relationship is also specified in respect to the R₃ substituent. All are within the ambit of this invention and in some of the most preferred compounds these stereochemical orientations are indicated. When the carbon atom in Formula I bearing an asterisk is of a defined and usually a D-configuration, diastereomers result according to the absolute configuration at the carbon atoms bearing the W, X, Y and R₃ groups. These diastereomers are arbitrarily referred to a diastereomers d₁, d₂, d₃, d₄, etc. and if desired, their independent syntheses or chromatographic separations may be achieved using standard methods or as described herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

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The instant compounds are generally isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic, methane sulfonic and the like. In addition, certain compounds containing an acidic function such as a carboxy can be isolated in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

The preparation of compounds of Formula I of the present invention can be carried out in sequential or convergent synthetic routes. Syntheses detailing the preparation of the compounds of Formula I in a sequential manner are presented in the following reaction schemes.

The phrase standard peptide coupling reaction conditions is used repeatedly here, and it means coupling a carboxylic acid with an amine using an acid activating agent such as EDC, DCC, and BOP in a inert solvent such as dichloromethane in the presence of a catalyst such as HOBT. The uses of protective groups for amine and carboxylic acid to facilitate the desired reaction and minimize the undesired reaction are well documented. Conditions required to remove protecting groups which may be present and can be found in Greene, T; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, NY 1991. CBZ and BOC were used extensively in the synthesis, and their removal conditions are known to those skilled in the art. Removal of CBZ groups can be achieved by a number of methods known in the art; for example, catalytic hydrogenation with hydrogen in the presence of a noble metal or its oxide such as palladium on activated carbon in a protic solvent such as ethanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, removal of CBZ groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid, or by treatment with a mixture of TFA and dimethylsulfide. Removal of BOC protecting groups is carried out in a solvent such as methylene chloride or

- 59 -

methanol or ethyl acetate, with a strong acid, such as trifluoroacetic acid or hydrochloric acid or hydrogen chloride gas.

5 The protected amino acid derivatives 1 are, in many cases, commercially available, where the protecting group L is, for example, BOC or CBZ groups. Other protected amino acid derivatives 1 can be prepared by literature methods (Williams, R. M. Synthesis of Optically Active α -Amino Acids, Pergamon Press: Oxford, 1989). Many of the piperidines, pyrrolidines and hexahydro-1H-azepines of formula 2 are either commercially available or known in the literature and others can be prepared following literature methods described for known compounds, some of which are described here. The skills required in carrying out the reaction and purification of the resulting reaction products are known to those skilled in the art. Purification procedures includes crystallization, and normal phase or reverse phase chromatography.

10

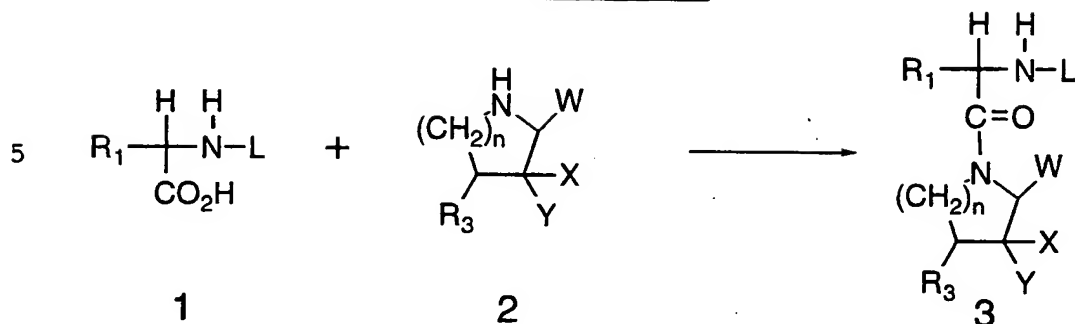
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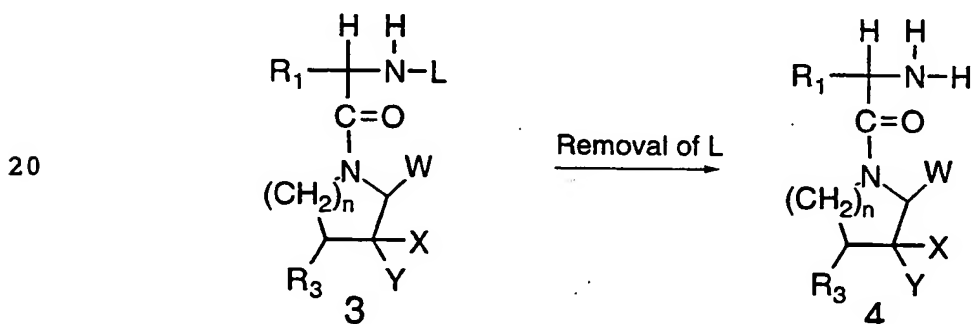
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- 60 -

SCHEME 1

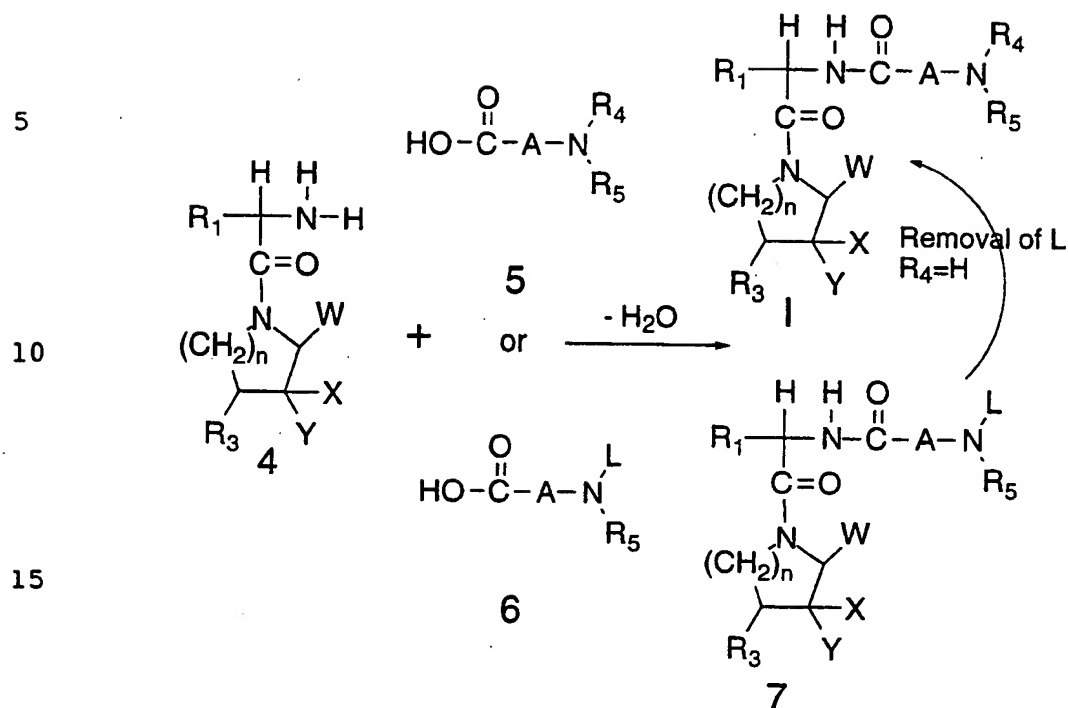
10 Intermediates of formula 3 may be synthesized as described in Scheme 1. Coupling of amine of formula 2, whose preparations are described later if they are not known compounds, to protected amino acids of formula 1, wherein L is a suitable protecting group, is conveniently carried out under standard peptide coupling conditions.

SCHEME 2

25 Conversion of 3 to intermediate 4 can be carried out as illustrated in Scheme 2 by removal of the protecting group L (CBZ, BOC, etc.) using standard methodology.

30

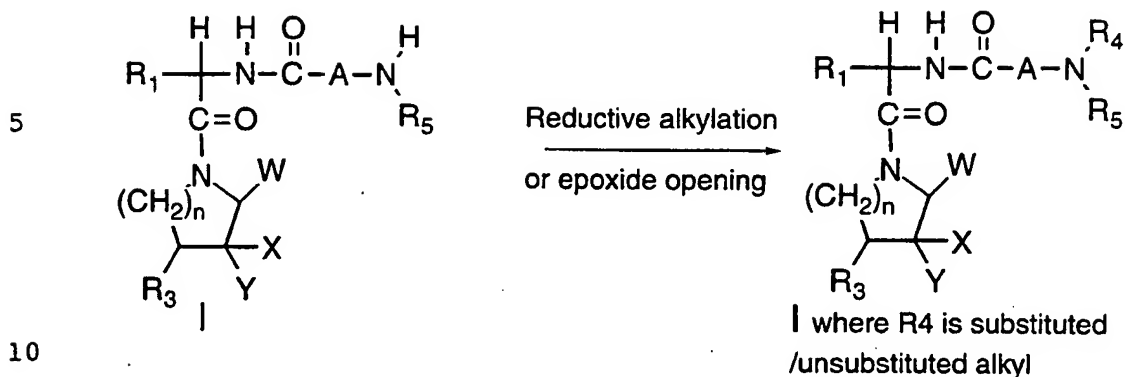
- 61 -

SCHEME 3

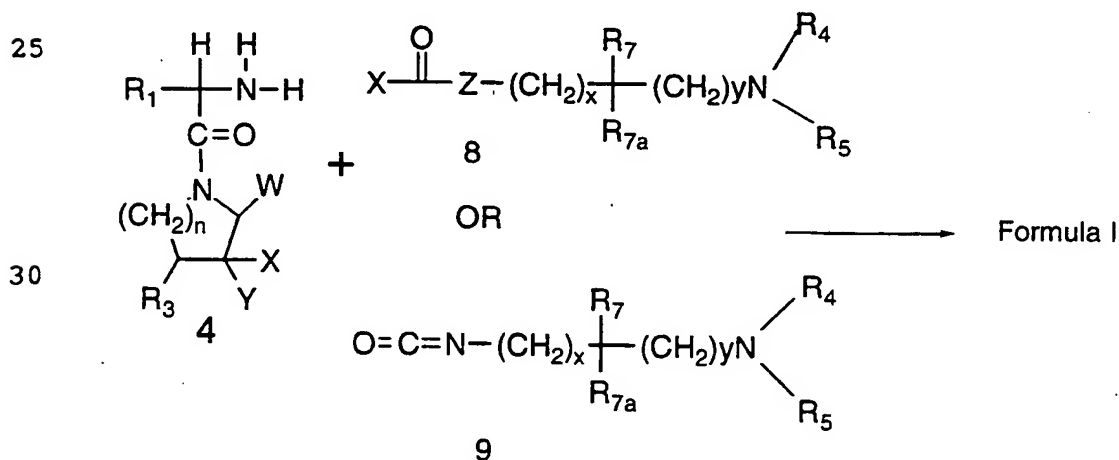
Intermediates of formula 5, wherein A is connected to the carbonyl by a carbon atom and thus A is $-(CH_2)_x-C(R_7)(R_{7a})-(CH_2)_y-$ can be prepared as shown in Scheme 3 by coupling intermediates of formula 4 to amino acids of formula 5 under the standard peptide coupling reaction conditions. The amino acids 5, as amino acid 1, are either commercially available or can be synthesized. Also if R_4 or R_5 is a hydrogen then the protected amino acids 6 are employed in the coupling reaction, wherein L is a protecting group as defined above. The removal of L in 7 to afford I, where $R_4 = H$, can be carried out under conditions known in the art.

30

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SCHEME 4

Compounds of formula I wherein R4 and/or R5 is a hydrogen can be further elaborated to new compounds I (with most preferred side chains R4 = CH₂-CH(OH)-CH₂X, wherein X = H or OH) which are substituted on the amino group as depicted in Scheme 4. Reductive alkylation of I with an aldehyde is carried out under conditions known in the art; for example, by catalytic hydrogenation with hydrogen in the presence of platinum, palladium, or nickel catalysts or with chemical reducing agents such as sodium cyanoborohydride in a protic solvent such as methanol or ethanol in the present of catalytic amount of acid. Alternatively, a similar transformation can be accomplished via an epoxide opening reaction.

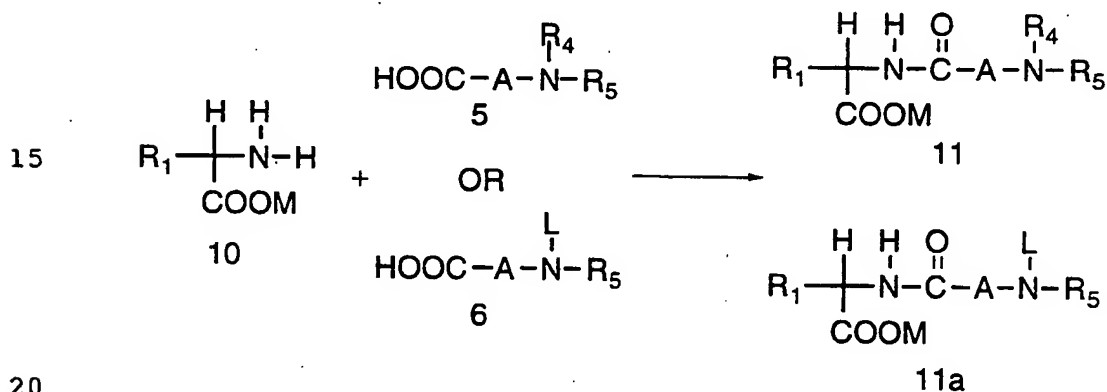
SCHEME 5

- 63 -

Compounds of formula I, wherein A is Z-(CH₂)_x-C(R₇)(R_{7a})-(CH₂)_y and Z is N-R₆ or O may be prepared as shown in Scheme 5 by reacting 4 with reagents 8, wherein X is a good leaving group such as Cl, Br, I, or imidazole. Alternatively, 4 can be reacted with an isocyanate of formula 9 in an inert solvent such as 1,2-dichloroethane to provide compounds of formula I where Z is NH.

The compounds of general formula I of the present invention may also be prepared in a convergent manner as described in Reaction Schemes 6, 7 and 8.

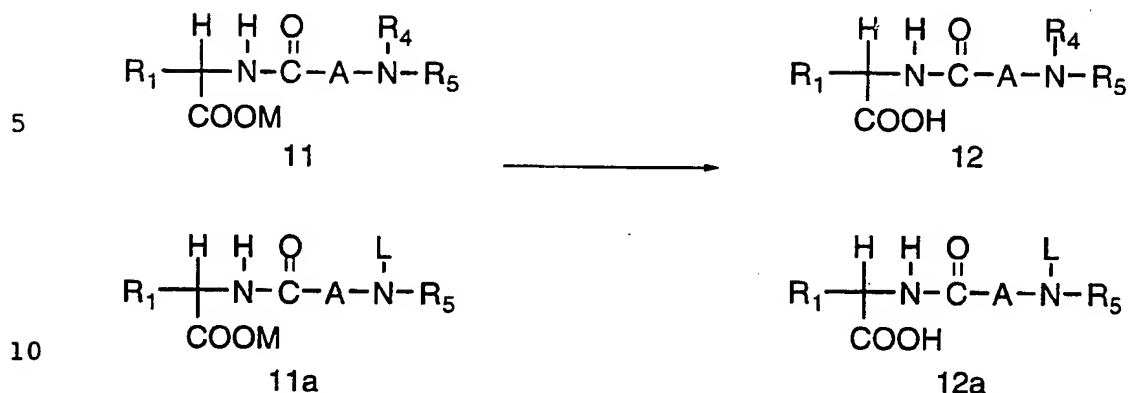
SCHEME 6



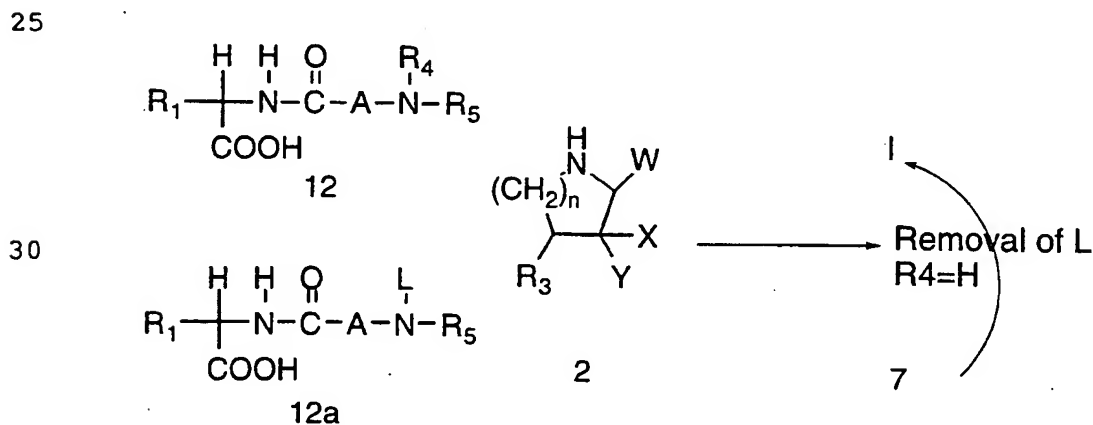
The carboxylic acid protected amino acid derivatives 10 are, in many cases, commercially available where M = methyl, ethyl, or benzyl esters. Other ester protected amino acids can be prepared by classical methods familiar to those skilled in the art. Some of these methods include the reaction of the amino acid with an alcohol in the presence of an acid such as hydrochloric acid or p-toluenesulfonic acid and azeotropic removal of water. Other methods includes the reaction of a protected amino acid with a diazoalkane, or with an alcohol and an acid activating agent such as EDC, DCC in the presence of a catalyst such as DMAP and removal of the protecting group L.

Intermediates of formula 11 or 11a, can be prepared as shown in Scheme 6 by coupling of amino acid ester 10 to amino acids of formula 6 or 7. When a urea linkage is present in 11 or 11a, it can be introduced as illustrated in Scheme 5.

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SCHEME 7

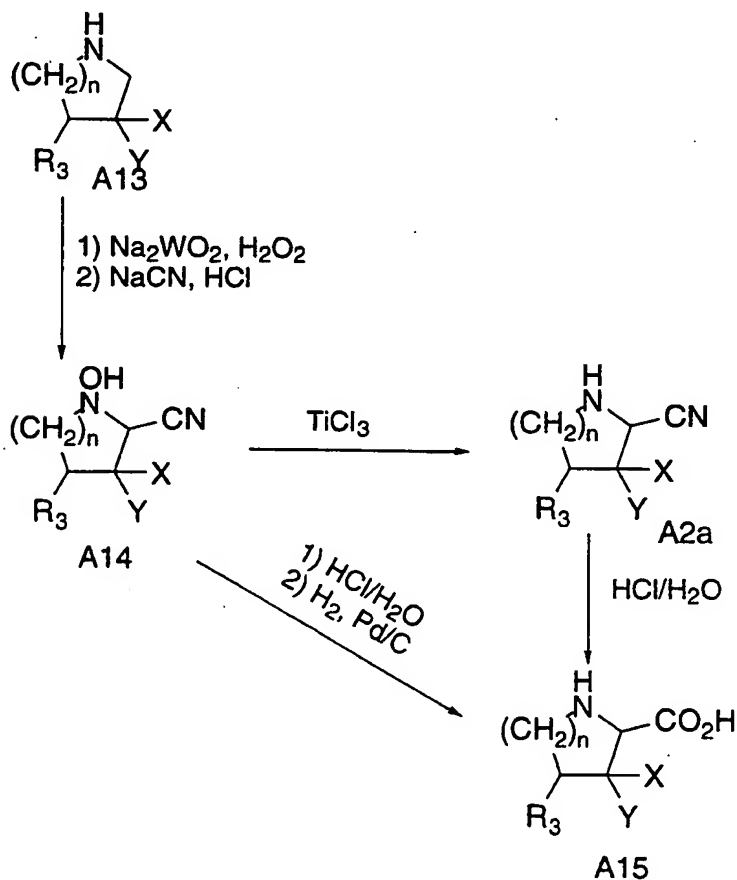
Conversion of the ester 11 or 11a to intermediate acids 12 or 12a can be achieved by a number of methods known in the art as described in Scheme 7; for example, methyl and ethyl esters can be hydrolyzed with lithium hydroxide in a protic solvent like aqueous methanol. In addition, removal of benzyl groups can be accomplished by a number of reductive methods including hydrogenation in the presence of palladium catalyst in a protic solvent such as methanol. An allyl ester can be cleaved with tetrakis-triphenylphosphine palladium catalyst in the presence of 2-ethylhexanoic acid in a variety of solvents including ethyl acetate and dichloromethane (see *J. Org. Chem.*, 42, 587 (1982)).

SCHEME 8

- 65 -

Acid 12 or 12a can then be elaborated to I or compound 7 as described in Scheme 8. Coupling of piperidines, pyrrolidines or hexahydro-1H-azepines of formula 2 to acids of formula 12 or 12a, wherein L is a suitable protecting group, is conveniently carried out under the standard peptide coupling reaction conditions. Transformation of 7 to I is achieved by removal of the protecting group L. When R₄ and/or R₅ is H, substituted alkyl groups may be optionally added to the nitrogen atom as described in Scheme 4.

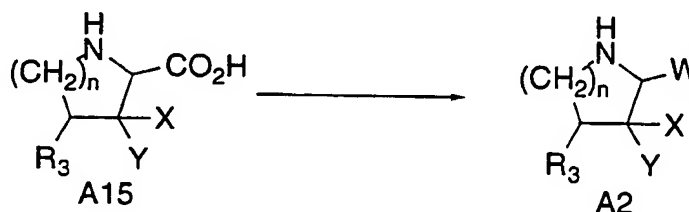
The 2-substituted piperidines, pyrrolidines or hexahydro-1H-azepines are either commercially available or can be prepared by literature procedures. Illustrated herein are some, but by no means all, the methods for their preparation.

SCHEME A9

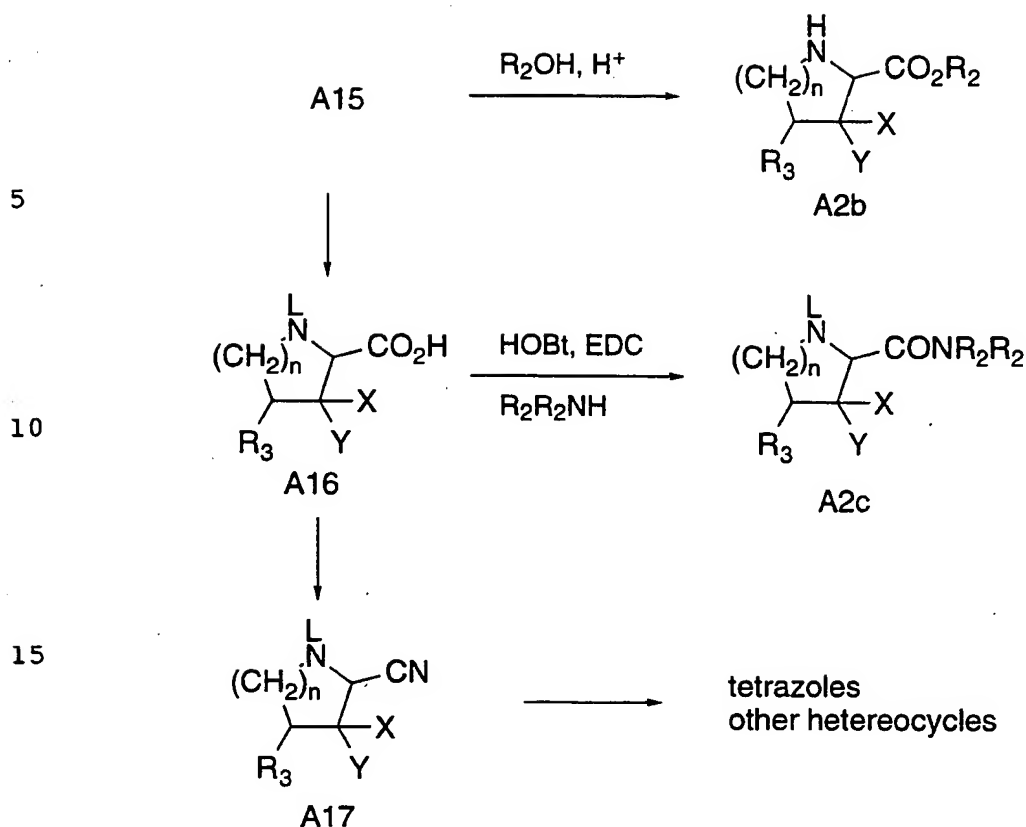
- 66 -

According to the protocol developed by S. Murahashi and T. Shiota (Tetrahedron Lett., 28, 6469-6472 (1987)) catalytic oxidation of cyclic amines such as piperidines, pyrrolidines or hexahydro-1H-azapines with hydrogen peroxide followed by treatment with hydrogen cyanide gives α -hydroxylaminonitriles of formula A14, which upon reduction (Murahashi, S.-I.; Koder, Y., Tetrahedron Letters, 26, 4633-4636 (1985)) give α -aminonitriles of formula A2a. In cases where X and Y are not both hydrogen and/or n is not 2, regioisomers and diastereoisomers may arise, and they may be separated by chromatography methods. Hydrolysis of the amino nitrile under acidic or basic conditions yields the amino acid. Alternatively, the hydroxylaminonitrile can be hydrolyzed first, then reduced by palladium catalyzed hydrogenation to afford the amino acid of formula A15. The amino acid and their derivatives prepared according to this method are racemic.

Alternatively, the nitrile A2a can be prepared by oxidation of the compound A13 to the imine as described in the literature (Goti and Romani in Tetrahedron Letters, 35, 6567-6570 (1994)) followed by reaction with cyanide. W can also be introduced by direct alkylation of the Boc protected compound A13 by butyl lithium followed by addition of electrophiles known as the Beak alkylation (Beak and Lee J. Org. Chem., 55, 2578-2580 (1990)). Asymmetric introduction of W can also be achieved by using a chiral catalyst (Kerrick and Beak, J. Am. Chem. Soc. 113, 9708-9710 (1991)).

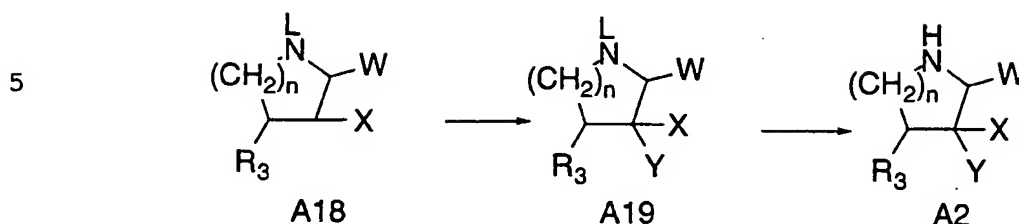
SCHEME A10

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The carboxylic acid functionality at the 2-position of compounds of formula A15 can be converted to ester, amide, nitrile, acyl sulfonamide, and moieties as defined by W to give compound of general formula 2 according to the conventional methods well documented in the literature and known to those skilled in the art (*The Practice of Peptide Synthesis*, by M. Bodanszky and A. Bodanszky, Springer-Verlag, 1984). L is an appropriate protecting group such as BOC, CBZ, etc. The carboxylic acid can also be converted into its next higher homologue, or to a derivative of the homologous acid, such as amide or ester by an Arndt-Eistert reaction. Alternatively, the ester can be directly homologated by the protocol using ynoate anions described by C. J. Kowalski and R. E. Reddy in *J. Org. Chem.*, 57, 7194-7208 (1992). The resulting acid and/or ester can be converted to the next higher homologue, and so on and so forth.

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SCHEME A11

10 Illustrated in Scheme A11 is a general method to introduce Y wherein X is an electron withdrawing group such as -CN, -CO₂R₈, where R₈ is alkyl, aryl, and alkyl(C₁-C₄)aryl are either known compounds or may be prepared by methods described above or by methods analogous to those used for the preparation of known

15 compounds. Introduction of the Y substitution can be achieved by first reacting compounds of formula A18 with a strong base such as potassium bis(trimethylsilyl)amide, lithium diisopropylamide following by addition of alkylating reagents such as alkyl halides, aryl alkyl halides, acyl halides, and haloformates in a inert solvent such as THF at temperatures from -100° to room temperature. Thio derivatives where the sulfur is

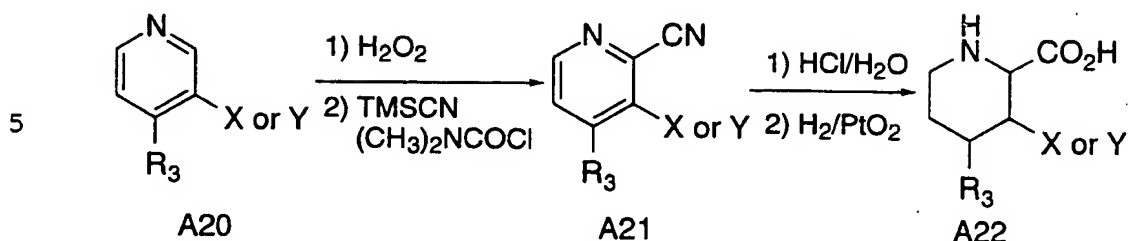
20 attached directly to an alkyl or an aryl group can be prepared similarly by reacting with a disulfide. The halides used in these reactions are either commercially available or known compounds in the literature can be prepared by methods analogous to those used for the preparation of known compounds. The protecting group L in compounds of formula

25 B19 can be removed with conventional chemistry to give compounds of formula 2.

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SCHEME A12

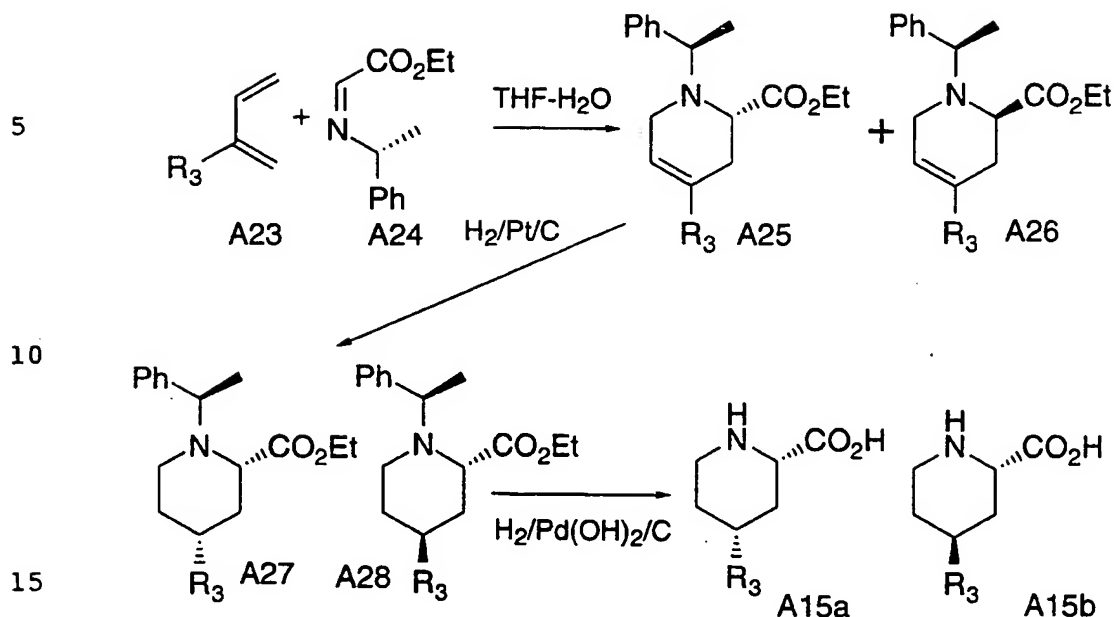


To prepare cis homoproline derivatives, the procedure described by Shuman et al can be used (Shuman, R. T.; Ornstein, P. L.; Paschal, J. W.; Gesellchen, P. D., *J. Org. Chem.*, **55**, 738-741 (1990)) (Scheme A12). Substituted pyridines of formula A20, many of them commercially available or prepared by literature procedures, are converted to their corresponding N-oxide by reacting with hydrogen peroxide. Reaction of the pyridine N-oxide with trimethylsilylcyanide and dimethylcarbamyl chloride gives the 2-nitrile of formula A21. If regioisomers should arise due to the presence of 3-substitution, they can be conveniently separated by chromatography. Hydrolysis of the nitrile to the acid under acidic or basic conditions followed by hydrogenation catalyzed by platinum oxide gives the piperidine carboxylic acid. The functionalization of the carboxylic acid is described above and in part by Scheme A10.

The amino acids generated by these synthetic protocols are racemic. However, procedures for resolving RS- α -amino acids by various methods are known in the literature (Toone, E. J. and Jones, J. B. *Can. J. Chem.*, **65**, 2722 (1987); Okamoto, S.; Hijikato, A. *Biochem. Biophys. Res. Commun.*, **101**, 440 (1981); Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Wiley: New York, **1961**, Vol. 1, 715-760). Therefore, the separated R- and S- isomers can be prepared by this methodology. Alternatively, the racemic piperidine, pyrrolidine and hexahydro-1H-azepine derivatives can be converted directly to growth hormone secretagogues or their intermediates, and the resulting diastereomeric mixtures can be separated at the appropriate stage by chromatography to yield the enantiomerically pure compounds.

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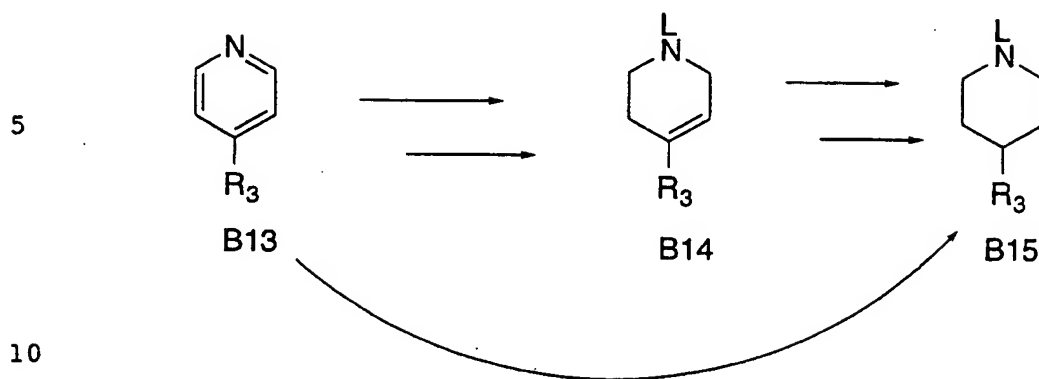
SCHEME A13



Alternatively, asymmetric synthesis can be carried out to synthesize optically pure piperidine, pyrrolidine and hexahydro-1H-azepine derivatives. For example, optically active piperidine-2-carboxylic acid derivatives A15a, A15b can be prepared by the aza-Diels-Alder reaction as described by Bailey et al (*J. Chem. Soc. Perkin Trans I*, 1337-1340 (1991)). Reaction between the chiral imine A23 and the diene A24 in the presence of TFA (1 equivalent) and water (catalytic) gives the adducts A25 and A26 with good diastereoselectivity. The two diastereoisomers can be separated, and each can be hydrogenated to reduce the double bond and to remove the chiral auxiliary. All four possible isomers can be achieved by this methodology. Illustrated here (Scheme A13) is the preparation of the two isomers A15a and A15b which have an S-configuration at the chiral center adjacent to the COOH. The two R- isomers at this center can be prepared similarly using compound A26.

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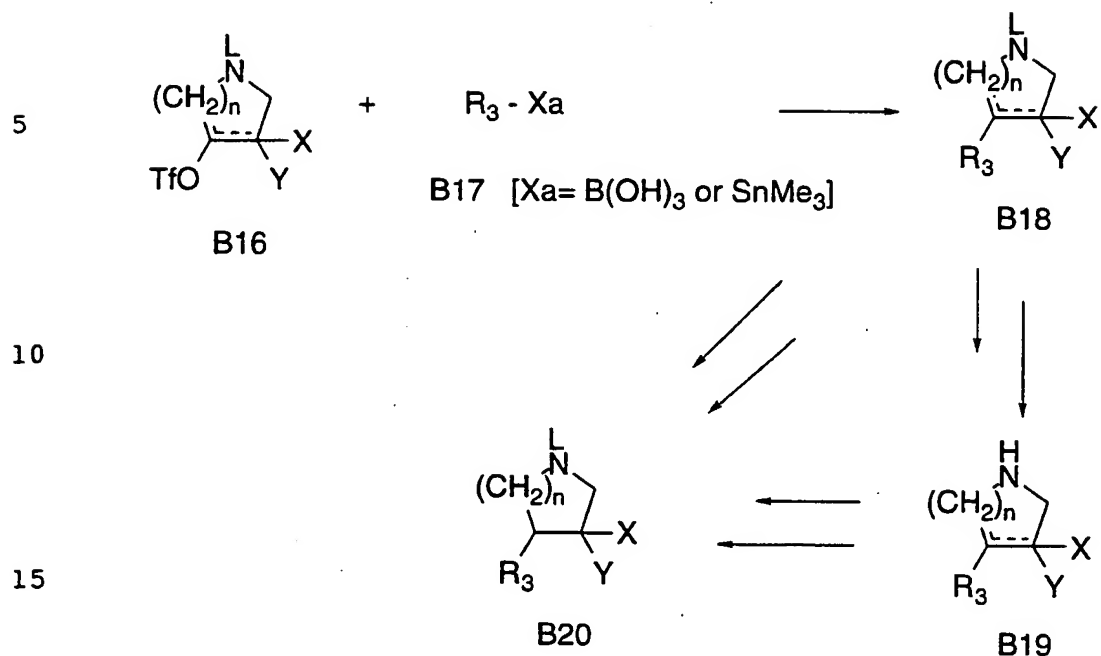
- 71 -

SCHEME B9

The synthesis of substituted piperidines of formula 2 ($n=2$) has been detailed in a number of research articles. For e.g., S. M. N. Efange et al. (J. Med. Chem., **36**, 1278-1283 (1993)) and M. S. Berridge et al. (J. Med. Chem., **36**, 1284-1290 (1993)) have used 4-substituted-pyridine intermediates B13 to synthesize 4-substituted tetrahydropiperidines of formula B14 (L = methyl) as detailed in Scheme B9. Removal of L from piperidines of formula B14 can be carried out by a number of methods familiar to those skilled in the art, including the cyanogen bromide protocol detailed by H. Ong et al. in J. Med. Chem., **23**, 981-986 (1983) and ACE-Cl method as described in R. Olofson et al. J. Org. Chem., **23**, 2795 (1984). For intermediates of formula B14, wherein L = Bn, simultaneous removal of the benzyl group and hydrogenation of the olefin can be accomplished by use of platinum or palladium catalysts in a protic solvent like methanol. Alternatively, B13 can be directly transformed to piperidines of formula B15 (L = H) by carrying out the reduction with platinum oxide in a protic solvent such as methanol with a catalytic amount of acid.

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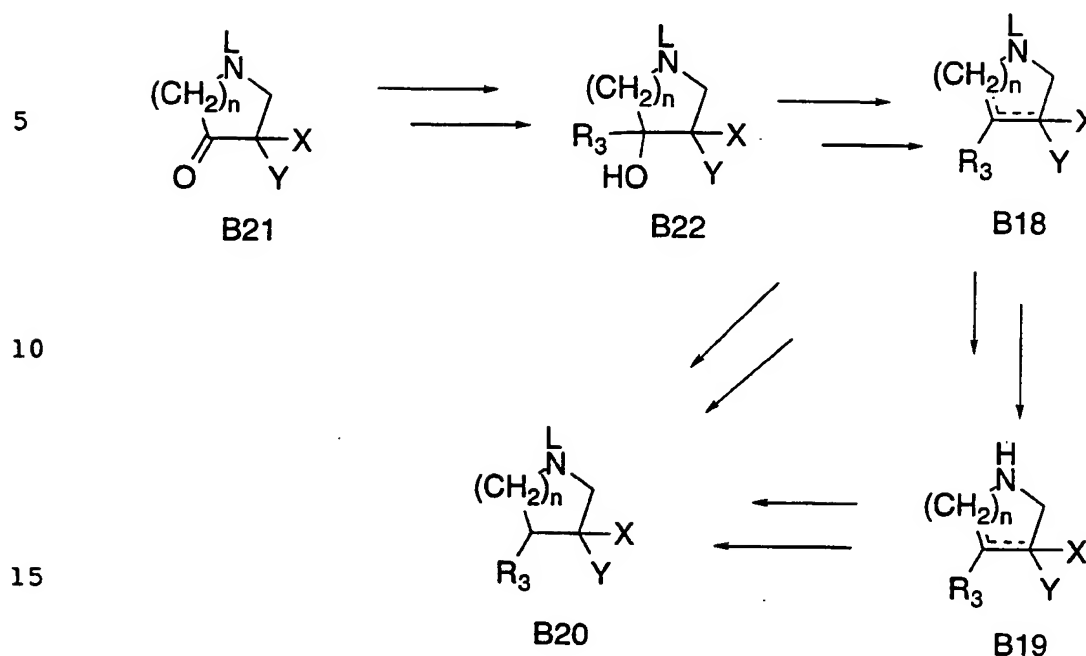
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SCHEME B10

Other methods as shown in Scheme B10 may also be used to synthesize compounds of formula 2. For example, cross-coupling of enol triflates of formula B16 (L = protecting group) where X and Y are defined in formula I with aryl boronic acids of formula B17 ($\text{Xa} = \text{B}(\text{OH})_3$) or aryl or phenyl or naphthyl tin reagents of formula B17 ($\text{Xa} = \text{SnMe}_3$) can be accomplished with palladium (II) or palladium (0) catalysts as detailed in the review article by W. J. Scott and J. E. McMurry *Acc. Chem. Res.*, 21, 47 (1988) to give in their examples tetrahydropiperidines B18 (L = protecting group). Various methods exist for the synthesis of the enol triflate intermediates of formula B16, phenyl or naphthyl boronic acids, and phenyl or naphthyl tin reagents of formula B17 ($\text{X} = \text{B}(\text{OH})_3$; SnMe_3) and are familiar to those skilled in the art.

Removal of the protecting group L furnishes for example, piperidines of formula B19 (L = H). Hydrogenation of B18 followed by removal of the protection group L also gives saturated derivatives B20. Alternatively, B19 can be transformed to compounds of formula B20 by hydrogenating the olefin in the presence of platinum or palladium catalysts in a protic solvent such as methanol.

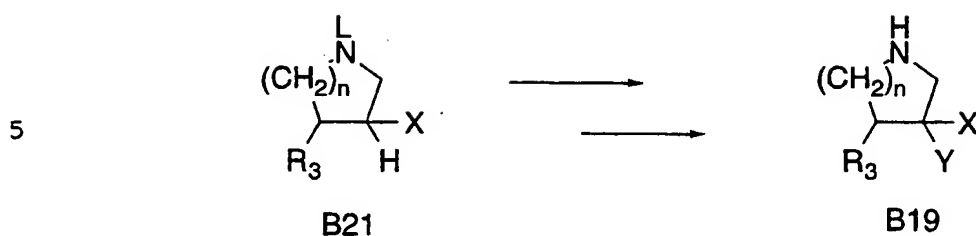
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SCHEME B11

Methods for the synthesis of substituted pyrrolidines, piperidines, and hexahydro-1H-azepines also involve addition of substituted and/or unsubstituted alkyl, cycloalkyl, phenyl or naphthyl Grignard reagents or lithium reagents to oxo-piperidines, oxo-pyrrolidines, or oxo-hexahydro-1H-azepines of formula B21 (L = benzyl, methyl, etc.) to give compounds of formula B22 (L = benzyl, methyl, etc.). The dehydration of the hydroxyl group of B22 (L = benzyl, methyl, etc.) to yield B18 (L = benzyl, methyl, etc.) can be carried out by treating it with strong acid or via an elimination reaction of the corresponding mesylate derived from B22 (L = benzyl, methyl, etc.). Compounds B18 can be transformed to B19 or B20 as described above.

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SCHEME B12

10 The 3,4-disubstituted piperidines, pyrrolidines and hexahydro-1H-azepines of formula B21 wherein X is an electron withdrawing group like an ester, ketone, nitrile, etc., can be further alkylated, hydroxylated, halogenated by using methods familiar to those skilled in the art. Once again, deprotection of the protecting group L can be carried out by methods familiar to those skilled in the art.

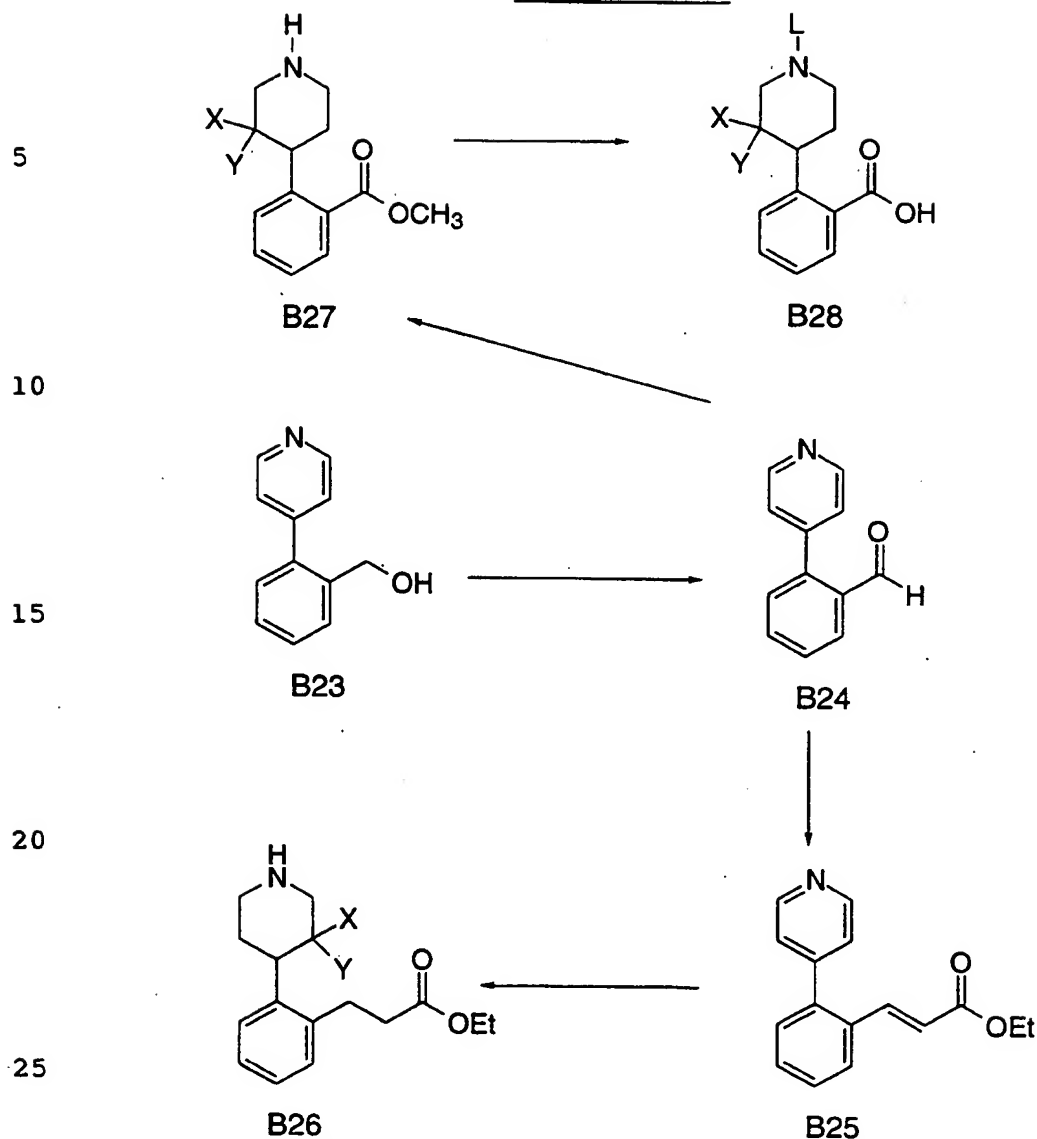
15 Specifically, ortho-substituted phenyl piperidines of formula B22a wherein X, Y = H can be prepared from the phenyl



25 piperidine intermediate B23 (see S. M. N. Efange et al. J. Med. Chem. , 26, 1278 (1993)).

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SCHEME B13

As shown in Scheme B13, the benzyl alcohol can be oxidized to aldehyde B24 by a variety of methods familiar to those skilled in the art. Commonly used methods are manganese dioxide in an inert solvent like chloroform or the Swern protocol. A variety of functional groups can now be elaborated from B24. For example, an Emmons reaction with triethylphosphonoacetate in the presence of base gives the α,β -unsaturated ester B25. Concurrent reduction of the pyridine unit and the olefin group with a platinum or palladium catalyst in an alcoholic solvent provides the piperidine of formula B26, wherein

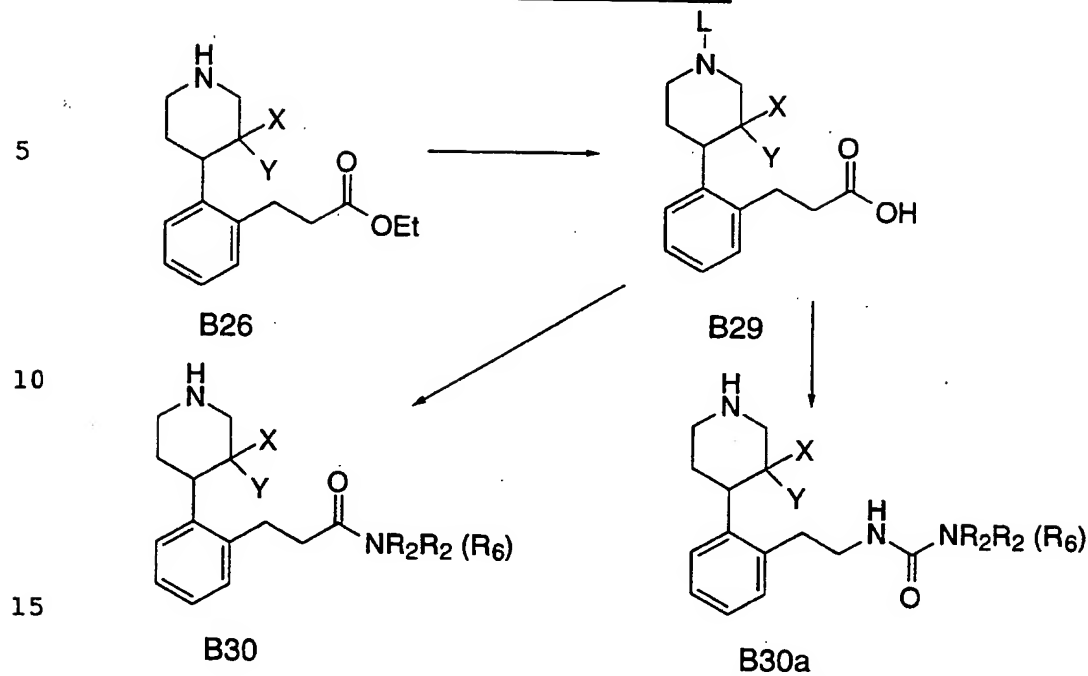
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X, Y = H. The piperidine B26 may be derivatized to ester and acid bearing compounds of formula I wherein X and Y=H by using chemistry detailed in Schemes 1-8. Alternatively, B24 can directly be transformed to a methyl ester B27, wherein X, Y = H, by oxidation of the aldehyde group to an ester with the Corey protocol (NaCN, acetic acid, MnO₂, in methanol) followed by reduction of the pyridine to a piperidine with platinum or palladium catalysts in a protic solvent like methanol. The piperidine B27 can be elaborated to compounds of Formula I by using chemistry detailed in Schemes 1-8. The piperidine unit of B27 can be protected by a variety of protecting groups L familiar to those skilled in the art and the ester unit can be hydrolyzed by well documented methods to give the acid B28, wherein X, Y = H. The acid intermediate B28 can be used to prepare compounds bearing a variety of highly functionalized piperidines that can be transformed to compounds of formula I.

Highly functionalized phenyl piperidines of formula B22, wherein X, Y = H, can be prepared by utilizing synthetic methods detailed below.

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SCHEME B14

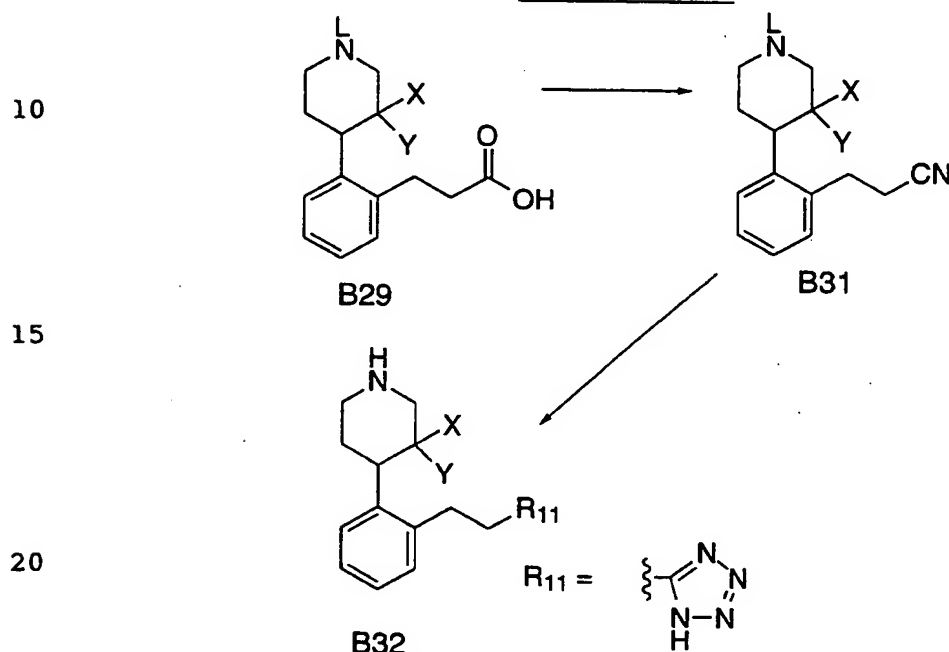


As depicted in Scheme B14 the piperidine B26 may also serve as a key intermediate for the synthesis of a variety of piperidines of formula B22a, wherein R_{10} may be alkyl and aryl amides, alkyl and aryl acylsulfonamides, alkyl and aryl ureas, alkyl and aryl carbamates, etc. The piperidine nitrogen of B26 can be protected with a protecting group L (commonly used groups include BOC, CBZ, FMOC) by well documented methods and the ester unit can now be hydrolyzed with sodium or potassium hydroxide in aqueous or alcoholic media to give B29. Peptide type coupling of B29 with primary and secondary aliphatic amines, aryl amines, suitably protected amino acids, alkyl or aryl sulfonamides provides amides of formula B30, wherein $X, Y = H$, followed by removal of the protecting group L. Alternatively, the acid B29 can be activated with carbonyl diimidazole and subsequently reacted with primary and secondary aliphatic amines, aryl amines, suitably protected amino acids, alkyl or aryl sulfonamides in an inert solvent like tetrahydrofuran or dimethylformamide to give amides of formula B30, wherein $X, Y = H$, L is on the nitrogen, and R_2 and R_6 may be any of the groups described in the scope of this invention. Ureas of formula B30a, wherein $X, Y = H$, L is on the nitrogen and R_2 and R_6 may be any of the

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groups described in the scope of this invention, can be synthesized from B29 by carrying out a Curtius rearrangement and trapping the isocyanate intermediate with amines of formula HNR_2R_2 or HNR_2R_6 . The protecting group L can be removed and elaborated to compounds of Formula I using chemistry presented in Schemes 1-8.

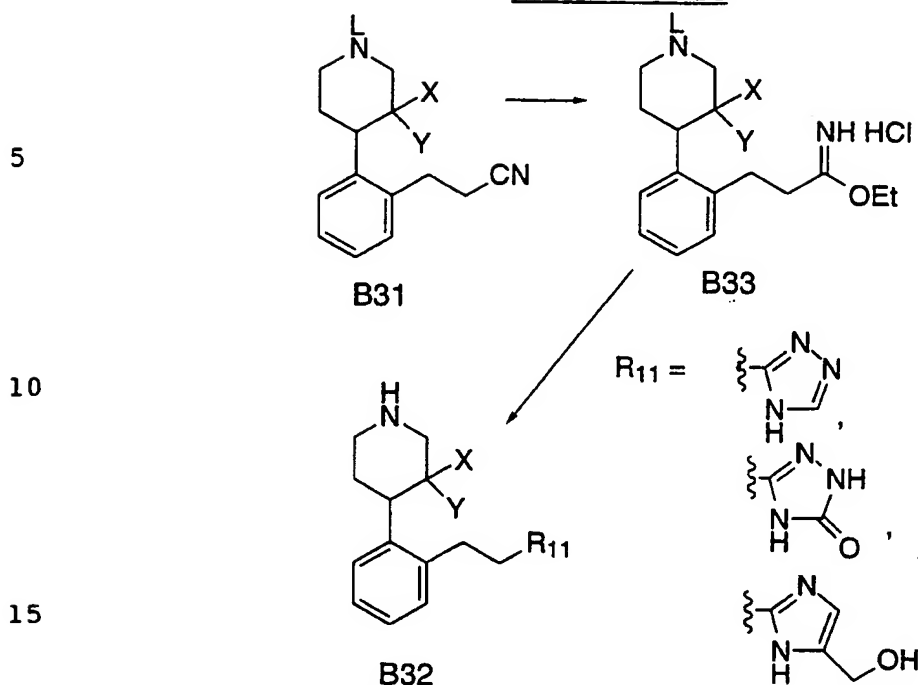
SCHEME B15



The acid intermediate B29 also serves as a key intermediate for the synthesis of heterocycle bearing compounds of formula B32, wherein X, Y = H. As shown in Scheme B15, the acid B29 can be transformed to a nitrile of formula B31, wherein X, Y = H, by a 3-step sequence involving activation of the acid with ethylchloroformate in the presence of a base like triethylamine, addition of aqueous ammonia to yield a primary amide, and dehydration of the amide to a nitrile with phosphorous oxychloride in pyridine. The nitrile intermediate B31 can now be transformed to a piperidine of formula B32 wherein X, Y = H and R_{11} is a 1H-tetrazole, by heating it with trimethyltin azide in an inert solvent like toluene or xylenes. The protecting group L may be removed and elaborated to compounds of formula I by using chemistry detailed in Schemes 1-8.

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SCHEME B16



Other heterocycle bearing piperidines of formula B32 can also be prepared from intermediate B31 as shown in Scheme B16.

Treatment of the nitrile B31 with anhydrous hydrochloric acid in dry ethanol gives imino-ether of formula B33. Addition of formyl hydrazine to B33 followed by heating of the intermediate in an inert solvent like toluene provides a piperidine of formula B32, wherein X, Y = H and R11 is a 1,2,4-triazole. Alternatively, carbomethoxyhydrazine can be added to imino-ether B33 and cyclized to provide B32, wherein X, Y = H and R11 is a triazolinone. Reaction of B33 with dihydroxyacetone in methanolic ammonia at high pressure gives B32, wherein X, Y = H and R11 is a hydroxymethyl imidazole. The protecting group L can be removed by methods familiar to those skilled in the art and elaborated to compounds of formula I by using chemistry detailed in Schemes 1-8.

Furthermore, acids, acid chlorides, nitriles, and imino-ethers serve as key intermediates in the preparation of a number of other alkyl, phenyl, hydroxy, and amino-substituted heterocycles. Many of the methods are documented in A.R. Katritzky, Handbook of Heterocyclic

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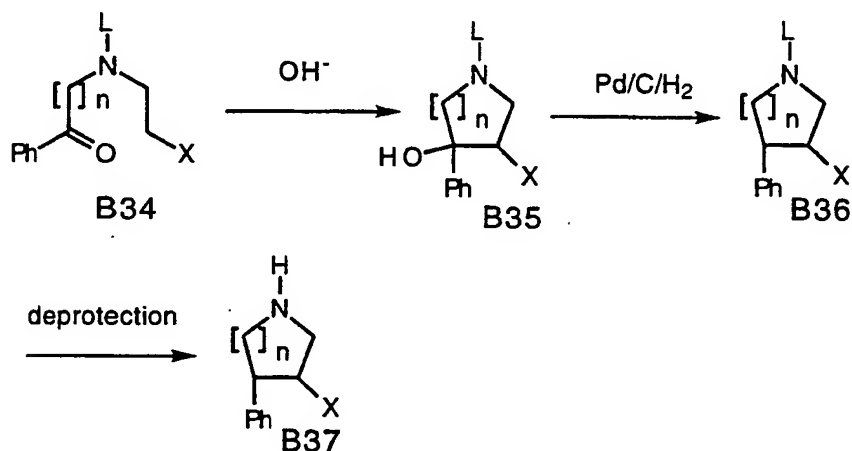
Chemistry, Pergamon Press, 1985, New York, New York, and may be used to synthesize a variety of heterocycle bearing compounds.

SCHEME B17

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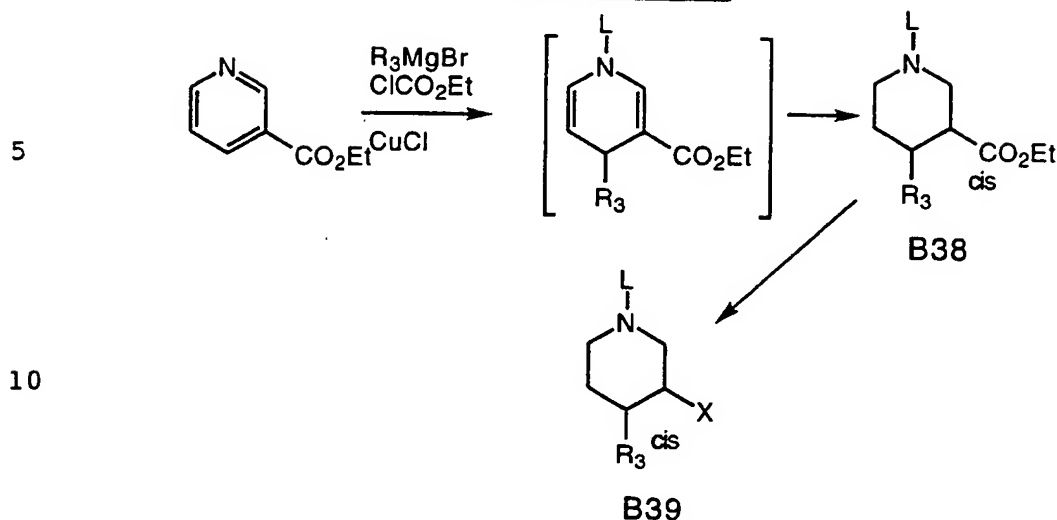
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Other applicable routes for the synthesis of mono- and di-substituted pyrrolidines, piperidines, and hexahydro-1H-azepines of formula II ($n=1$ or 2) are known in the literature. For example, J. J. Plati and W. Wenner (*J. Org. Chem.*, **14**, 543 (1949)) have demonstrated that the ketoamine intermediate B34 may be elaborated to B35 ($n=1, 2, 3$) under aldol condensation conditions. Dehydroxylation of B35 can be achieved by a number of methods including a catalytic hydrogenation method that utilizes palladium catalysts in a protic solvent like methanol. Removal of L from B36 can be carried out methods, including the ACE-Cl method as described in R. Olofson et al. (*J. Org. Chem.*, **43**, 2795 (1984)).

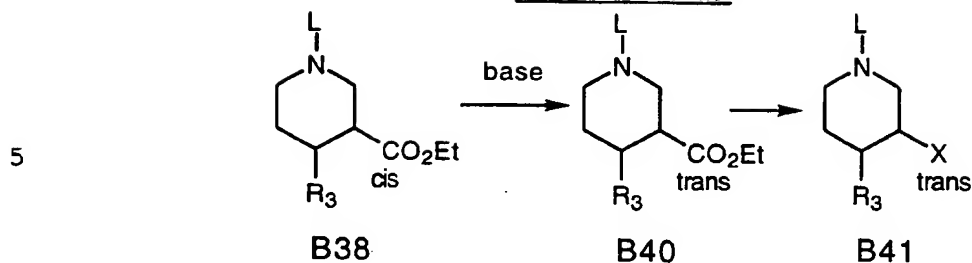
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SCHEME B18

The synthesis of 3,4-disubstituted piperidines of formula 2 ($n=2$) can be conveniently prepared by literature procedures. Illustrated below is one of these general methods. G. T. Borrett has demonstrated the synthesis of *cis* 3,4-disubstituted piperidine B39 (US Patent 4,861,893) from the commercially available ethyl nicotinate and the Grignard reagent R_3MgBr where R_3 is defined in formula I. The ester functionality of B38 may be further modified through conventional chemistry to provide other functional groups X as defined in the scope of the invention. Illustrated here are some, but by no means all, the methods available to prepare functional groups X. For example, the ester of B38 can be hydrolyzed to give the corresponding carboxylic acid B39 ($X=CO_2H$); B39 may then be converted to amides ($X=CONR_2R_2$) by a simple peptide-type coupling reaction, to ureas or carbamates ($X=NC(O)NR_2R_2$, $NC(O)OR_2$) by the Curtius rearrangement (Smith, Org. React., 3, 337 (1946)) followed by trapping of the isocyanate intermediate with amines or alcohols or to an hydroxymethyl unit ($X=CH_2OR_2$) by borane reduction. The acid B39 can also be converted to a nitrile and then elaborated to heterocyclic compounds ($X=tetrazolyl$, $triazolyl$, $triazolinolyl$ etc.) by the procedures described in Schemes B15 and B16. The carboxylic acid B39 ($X=CO_2H$) can also be converted into its higher homologue B39 ($X=CH_2CO_2H$) by an Arndt-Eistert reaction and further derivatized by methods which have been described above.

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SCHEME B19

The cis 3,4-disubstituted piperidines B38 can be converted to trans 3,4-disubstituted piperidines B40 as shown in Scheme B19 by treating B38 with a catalytic amount of base such as sodium ethoxide in protic solvent. Once again, the ester functional group of B40 can be further modified by methods familiar to those skilled in the art, including the procedures described in Scheme B18. The protecting group L from compounds of formulas B39 and B41 can be removed through conventional chemistry and elaborated to compounds of formula I by using chemistry described above.

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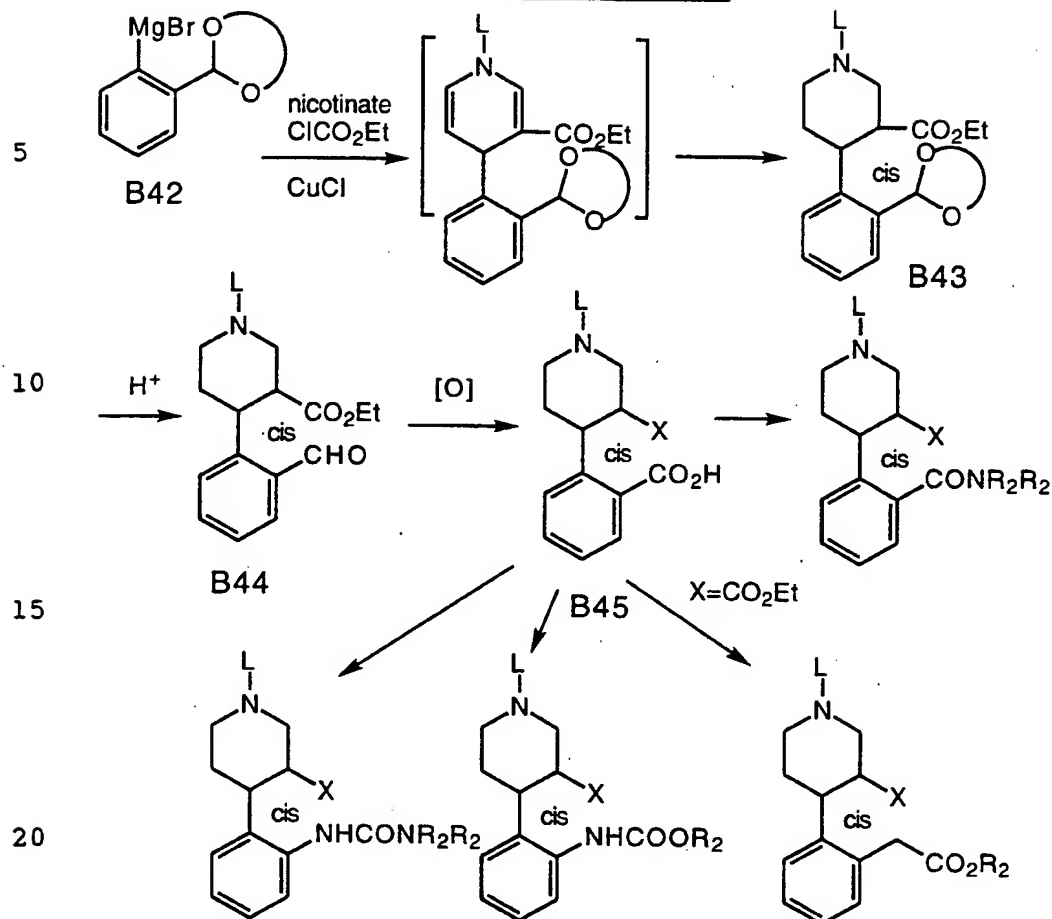
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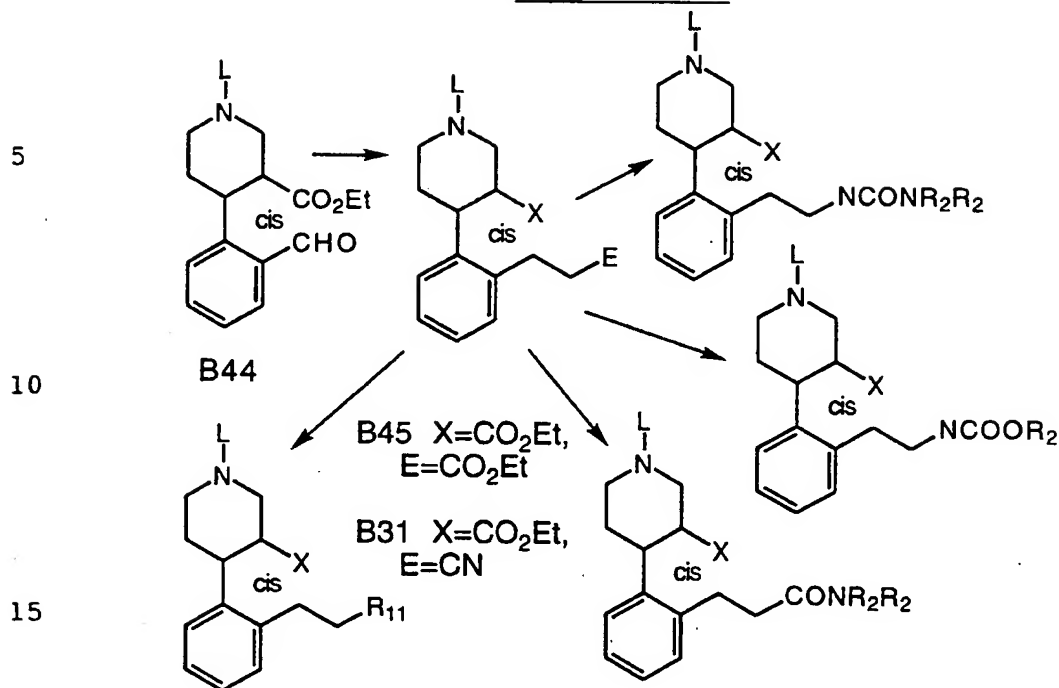
SCHEME B20



As described in Scheme B20, cis 3,4-disubstituted piperidines of formula B43 can be prepared by the addition of B42 to ethyl nicotinate by the procedure of G.T. Borrett (U.S. Patent No. 4,861,893). The acetal protecting group can be removed by a number of methods familiar to those skilled in the art. The resulting aldehyde B44 serves as a key intermediate for the synthesis of highly functionalized 3,4-disubstituted piperidines. The aldehyde B44 can be oxidized to the corresponding carboxylic acid B45 and then further elaborated to a variety of functional groups such as amides, ureas, carbamates, acylsulfonamides and etc. Some examples of these transformations are discussed in connection with Scheme B14.

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SCHEME B21



Compound B44 can also be converted to an α , β -unsaturated ester or nitrile by an Emmons reaction. The resulting unsaturated ester or nitrile can be hydrogenated using a catalytic amount of palladium or platinum under hydrogen atmosphere. The diester B45 (X=CO₂Et, E=CO₂Et) as shown in Scheme B21 can be selectively hydrolyzed to corresponding acid B45 (X=CO₂Et, E=CO₂H) which can be further elaborated to variety of functional groups by a number of methods. Compounds of formula B31 (X=CO₂Et, E=CN) can be transformed to compounds of formula 32 (X=CO₂Et, Y=H, R₁₁=1H-tetrazole) by heating B31 with trimethyl azide in toluene. Alternately, the nitrile intermediate B31 (for example, with X=CO₂Et, E=CN) may also serve as a synthetic precursor for the synthesis of heterocycle bearing compounds of formula B32 (X=CO₂Et). Many of the synthetic methods as noted above in A.R. Katritzky, *Handbook of Heterocyclic Chemistry*, Pergamon Press, 1985, New York, New York, and are discussed in connection with Scheme B16.

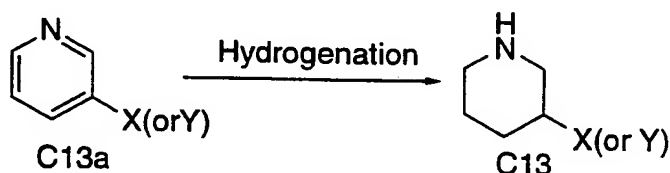
The 3,4-disubstituted compounds 2 generated by these synthetic protocols are racemic. Mono and disubstituted pyrrolidines and

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hexahydro-1H-azepines 2 generated by these synthetic protocols are also racemic. Chiral intermediates of formula 2 are available by numerous methods including by the classical resolution of racemates. For example resolution can be achieved by the formation of diastereomeric salts of racemic amines with optically active acids such as D- and L- tartaric acid. The determination of the absolute stereochemistry can be accomplished in a number of ways including X-ray crystallography of a suitable crystalline derivative such as a D- or L- tartaric acid salt. Alternatively, asymmetric synthesis can be carried out to synthesize optically pure compounds.

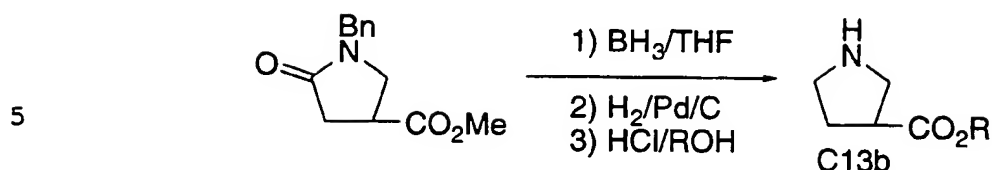
Furthermore, the racemic intermediates of formula 2 can be derivatized with chiral reagents and these products may be separated by chromatography and chiral compounds of formula 2 may be regenerated from them by hydrolysis, or as stated earlier, racemic intermediates of formula 2 can be converted directly to growth hormone secretagogues, and the resulting diastereomeric mixtures can be separated by chromatography to yield the enantiomerically pure compounds.

SCHEME C9



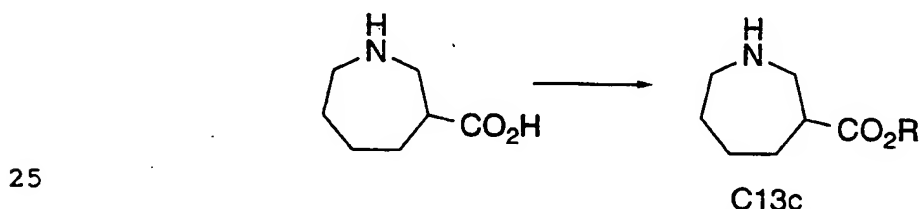
3-Monosubstituted piperidines of formula C13 can be prepared by the reduction of pyridine derivatives or their salts by hydrogenation in a suitable organic solvent such as water, acetic acid, alcohol, e.g. ethanol, or their mixture, in the presence of a noble metal catalyst such as platinum or an oxide thereof on a support such as activated carbon, and conveniently at room temperature and atmospheric pressure or under elevated temperature and pressure. 3-Monosubstituted piperidines can also be prepared by modification of the X or Y moiety of the existing 3-monosubstituted piperidines.

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SCHEME C9A

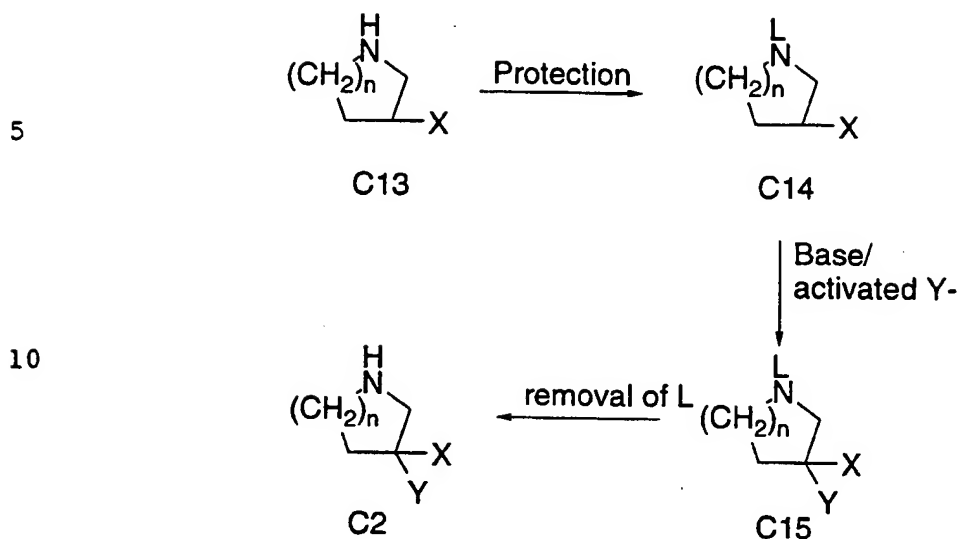
3-Monosubstituted pyrrolidines are commercially available or can be conveniently prepared by literature procedures. Shown in Scheme C9A is an example of the preparation of these compounds via pyrrolidine-3-carboxylic acid ester. The commercially available compound methyl 1-benzyl-4-oxo-3-pyrrolidinecarboxylate is reduced by borane (*J. Chem. Soc.*, 24, 1618-1619). Removal of the benzyl group by catalytic hydrogenolysis followed by ester exchange in an appropriate alcohol medium such as ethyl alcohol in the presence of acid gave the compound C13b. The ester functionality may be further modified through conventional chemistry to other groups as defined by X. 3-Monosubstituted pyrrolidines may also be prepared by catalytic hydrogenation of 3-substituted pyrroles.

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SCHEME C9B


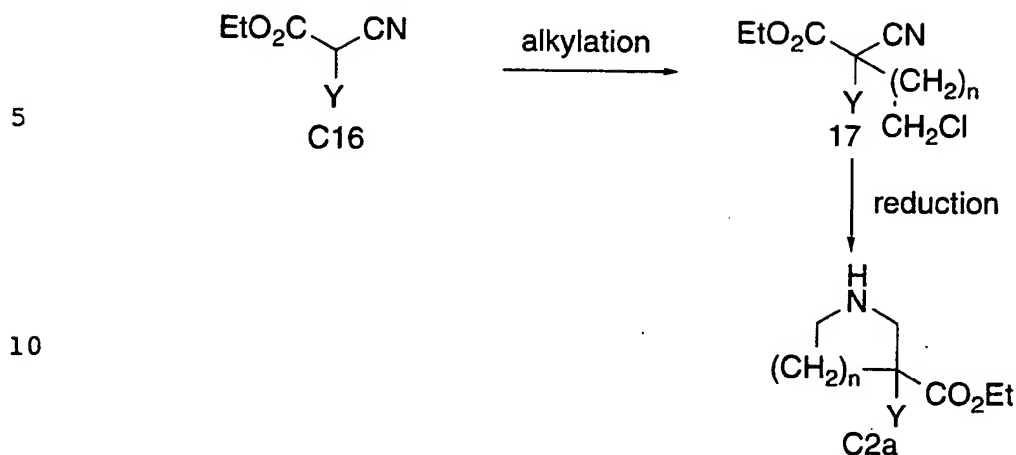
Hexahydro-1H-azepines are commercially available or may be prepared by the literature procedure. Hexahydro-1H-azepine-3-carboxylic acid (Krogsgaard-Larsen, P. et al., *Acta. Chem. Scand.*, B32, 327, (1978)) is esterified in an alcohol solvent in the presence of acid. The ester functionality may be further modified through conventional chemistry to other groups within the definition of X.

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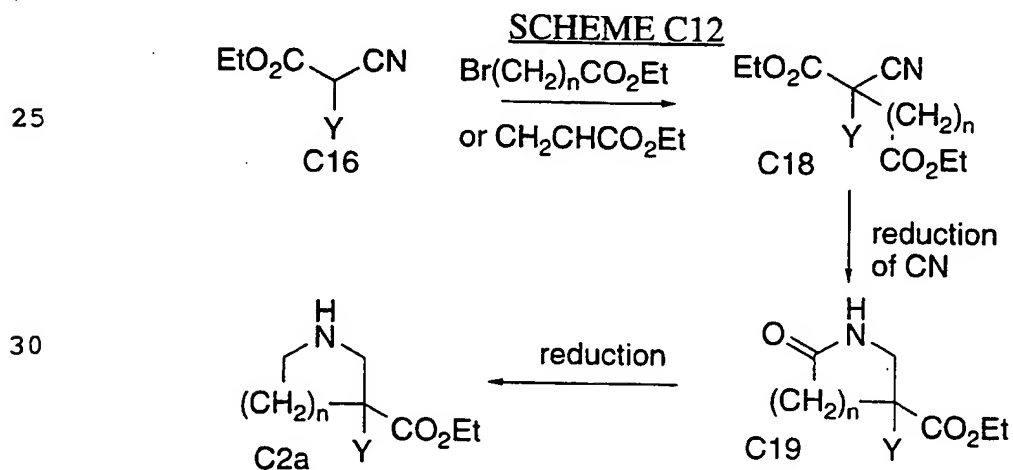
SCHEME C10

Illustrated in Scheme C10 is a general way to prepare di-substituted piperidines, pyrrolidines, and hexahydro-1H-azepines. Compounds of Formula C13 wherein X is an electron withdrawing group such as -CN, -CO₂R₈, where R₈ is alkyl, aryl, and (C₁-C₄alkyl)aryl are known compounds or may be prepared by methods analogous to those used for the preparation of such known compounds. The secondary amine of compounds of Formula C13 may be first protected by a protecting group L such as BOC and CBZ using the conventional techniques. Introduction of the Y substitution can be achieved by first reacting compounds of Formula C14 with a strong base such as lithium bis(trimethylsilyl)amide, lithium diisopropylamide following by addition of alkylating or acylating reagents such as alkyl halides, aryl alkyl halides, acyl halides, and haloformates in a inert solvent such as THF at temperatures from -100° to room temperature. Thio derivatives where the sulfur is attached directly to an alkyl or an aryl group can be prepared similarly by reacting with a disulfide. The halides used in these reactions are either commercially available or known compounds in the literature or may be prepared by methods analogous to those used for the preparation of known compounds. The protecting group L in compounds of formula C15 may be removed with conventional chemistry to give compounds of Formula 2.

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SCHEME C11

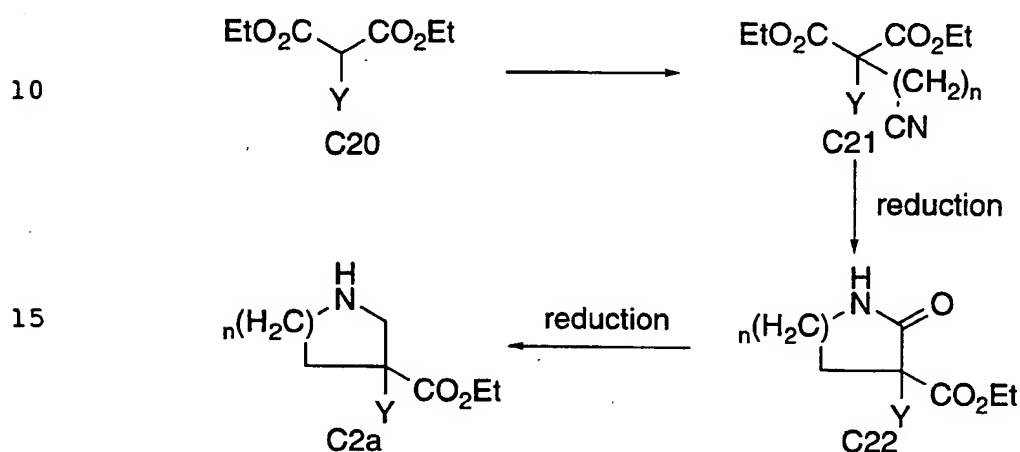
Alternative ways of preparing compounds of Formula 2 include construction of the ring itself (Jacoby, R. L. et al, J. Med. Chem., 17, 453-455, (1974)). Alkylation of the cyanoacetates of general formula C16, which are commercially available or may be prepared from literature procedures, with alkyl dihalides such as 1-bromo-2-chloroethane or 1-bromo-3-chloropropane yields the chloride C17. Reduction of the nitriles C17 by borane or by hydrogenation using Raney Ni as a catalyst gives the corresponding primary amines, which upon refluxing in ethanol to give compounds of Formula 2a.



Alternatively, the cyanoacetates of general formula C16 may be alkylated with an ethoxycarbonylalkyl bromide or reacted with ethyl

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acrylate to give compounds of Formula C18. Reduction of the nitriles C18 by borane or by hydrogenation using Raney Ni as a catalyst gives the corresponding primary amines, which upon refluxing in ethanol gives lactam C19. Reduction of the lactam C19 by borane gives compounds of Formula C2a.

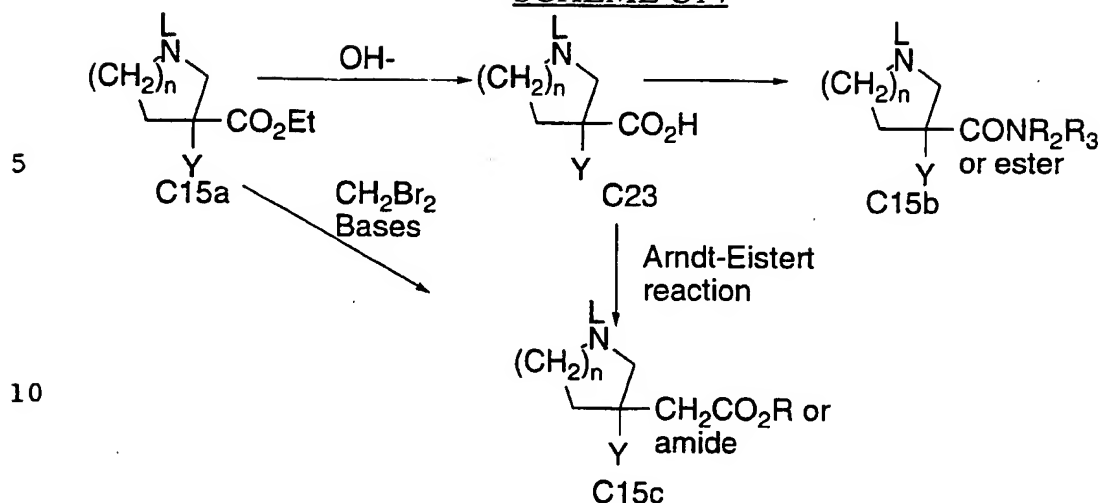
SCHEME C13

20 Alternatively, a malonate of general formula C20 may be alkylated with cyanoalkyl bromide or can be reacted with acrylonitrile to form compounds of formula C21. Reduction of the nitriles C21 by borane or by hydrogenation using Raney Ni as a catalyst gives the corresponding primary amines, which upon refluxing in ethanol gives lactam C22. Reduction of the lactam C22 by borane gives compounds of formula C2a.

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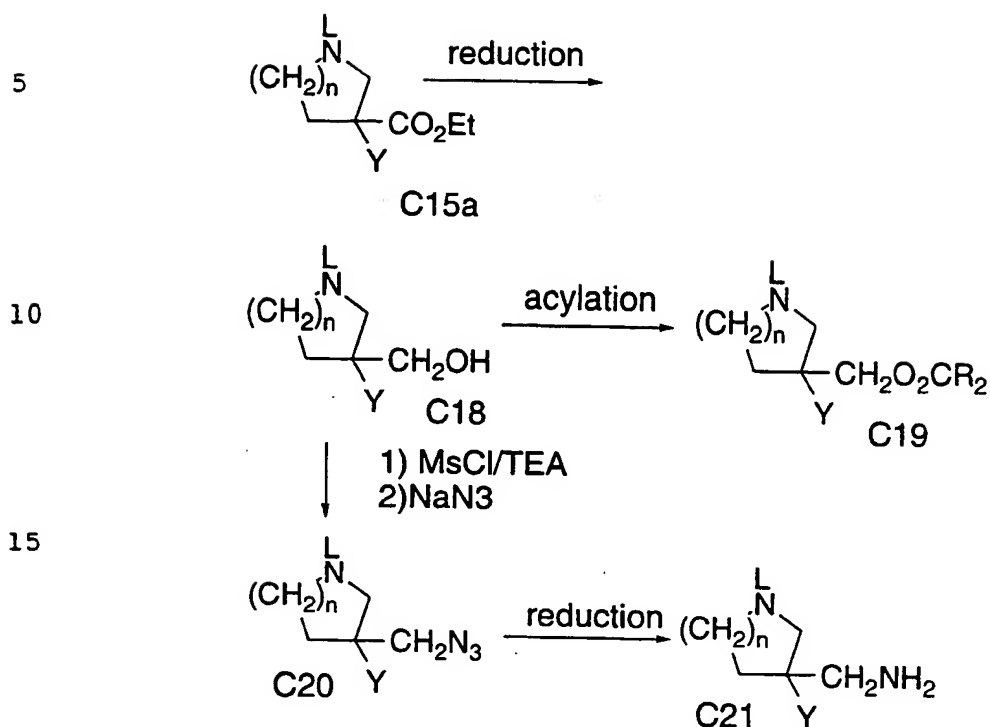
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SCHEME C14



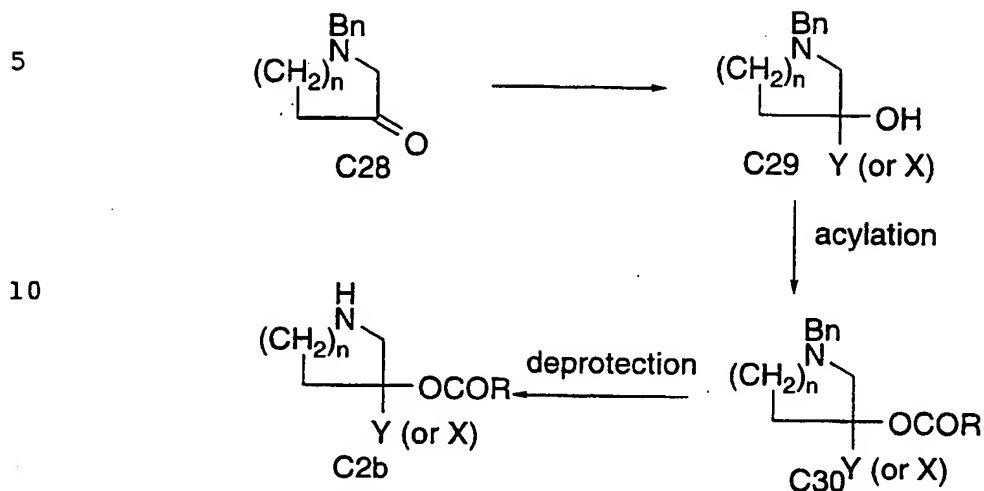
The X, Y functionalities in compounds of general structure C15 may be further elaborated to groups not accessible by direct alkylation. For example in Compound C15 when X = CO₂Et the ester (provided that this is the only ester group in the molecule) can be saponified to the carboxylic acid, which can be further derivatized to amides or other esters. The carboxylic acid can be converted into its next higher homologue, or to a derivative of the homologous acid, such as amide or ester by an Arndt-Eistert reaction. Alternatively, the ester can be directly homologated by the protocol using ynolate anions described by C. J. Kowalski and R. E. Reddy in *J. Org. Chem.*, **57**, 7194-7208 (1992). The resulting acid and/or ester may be converted to the next higher homologue, and so on and so forth. The protecting group L may be removed through conventional chemistry.

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SCHEME C15

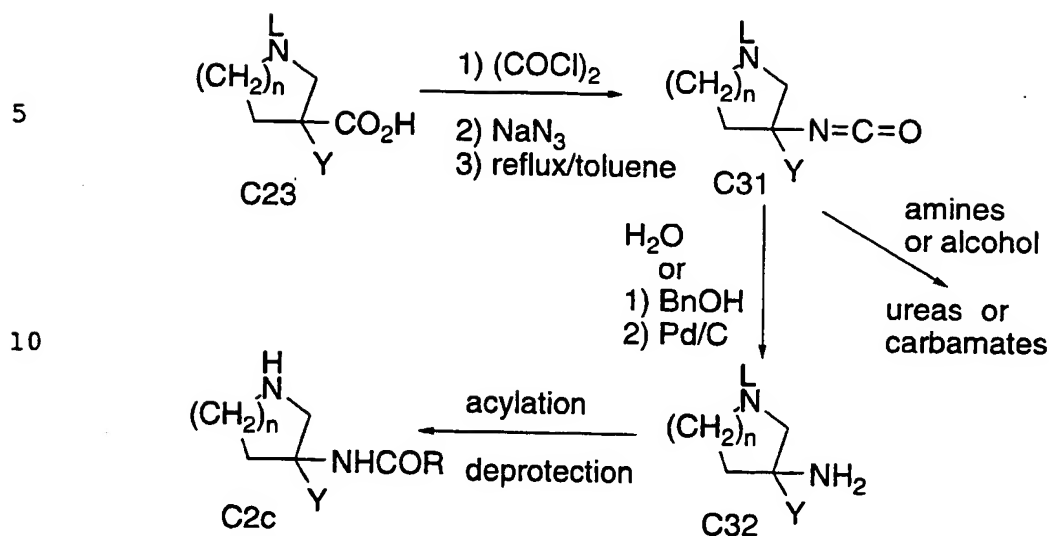
The ester in C15a may be reduced to an alcohol C18 in a suitable solvent such as THF or ether with a reducing agent such as DIBAL-H and conveniently carried out at temperatures from -100°C to 0°C. The alcohol may be acylated to Compound C19 in a suitable solvent such as dichloromethane using an acyl halide or acid anhydride in the presence of a base such as triethyl amine (TEA). The hydroxy group in C18 may also be converted to a good leaving group such as mesylate and displaced by a nucleophile such as cyanide, a thiol or an azide. Reduction of the azide in compounds of Formula C20 to an amine C21 can be achieved by hydrogenation in the presence of a noble metal such as palladium or its oxide or Raney nickel in a protic solvent such as ethanol. The nitrile can be reduced to afford the homologous amine. The amine of Formula C21 may be further elaborated to amides, ureas sulfonamides as defined by X through conventional chemistry. The protecting group L may be removed through conventional chemistry.

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SCHEME C16

In cases where oxygen is directly attached to the ring, a convenient method involves the addition reaction by an activated form of an alkyl, aryl, alkylaryl group, such as lithium reagent, Grignard reagents, and the like with a ketone of general formula C28, which is commercially available. Further derivatization of the resulting hydroxy group by acylation, sulfonylation, alkylation, and the like gives compounds as defined by Y or X through conventional chemistry. Removal of the benzyl protective group may be carried out under the usual conditions to give compounds of general formula C2b. Shown in Scheme C16 is a general example of acylations.

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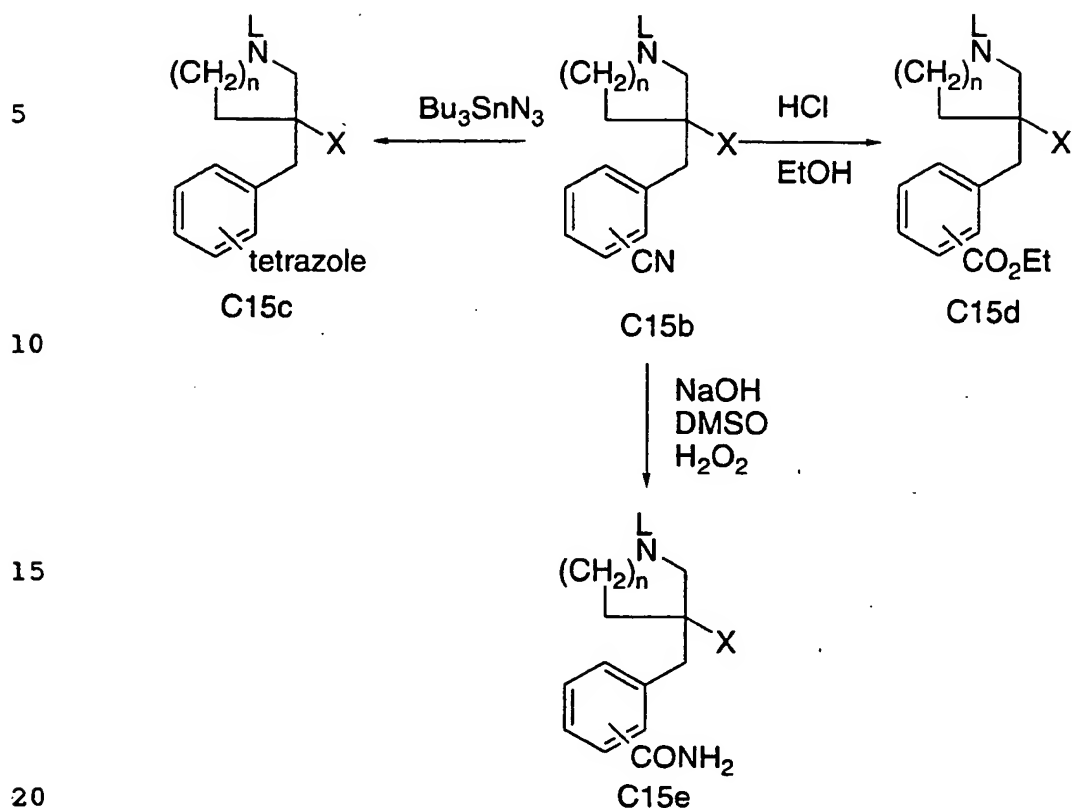
SCHEME C17

15 In cases where a nitrogen-substituted group is directly attached to the ring, a convenient method is to use the Curtius rearrangement on the acid C23 to afford the isocyanate C31. Addition of amines or alcohols give ureas or carbamates respectively which can be deprotected to remove L to give special cases of compounds of formula C2. Conversion of the isocyanate to amine by hydrolysis gives compound C32. Further

20 derivatization of the resulting amine group by acylation, sulfonylation, alkylation, and the like to give compounds as defined by Y or X can be done through conventional chemistry. Removal of the protective group L may be carried out under the usual conditions to give compounds of

25 general formula C2c. Shown in Scheme C17 is a general example of acylations.

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SCHEME C18

For compounds that are not readily obtainable by direct alkylation as shown in Scheme C10, modifications of easily obtainable compounds of general formula C15 may be conducted to achieve the desired substitution through conventional chemistry. For example, compounds with Y being hydroxybenzyl may be prepared by demethylation of the corresponding compound wherein Y is methoxybenzyl. Similarly, compounds with Y being aminobenzyl may be prepared by reduction of the corresponding compound wherein Y is nitrobenzyl. Shown in Scheme C18 is an example of a procedure that uses nitrile as a starting point for the preparation of compounds with different substitutions. Removal of the protective group L gives compounds of general formula C2 as described in Scheme C10.

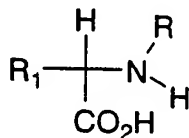
Compounds of the general formula C2 prepared in this way are racemic when X and Y are not identical. Resolution of the two enantiomers can be conveniently achieved by classical crystallization

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methods by using a chiral acid such as L- or D-tartaric acid, (+) or (-)-10-camphorsulfonic acid in a suitable solvent such as acetone, water, alcohol, ether, acetate or their mixture. Alternatively, the racemic amine C2 can be reacted with a chiral auxiliary such as (R) or (S)-O-acetylmandelic acid followed by chromatographic separation of the two diastereomers, and removal of the chiral auxiliary by hydrolysis. Alternatively asymmetric alkylation can also be utilized for the synthesis of optically active intermediate by introducing a removable chiral auxiliary in X or in place of L with subsequent chromatographic separation of diastereomers.

In cases where a sulfide is present in the molecule, it may be oxidized to a sulfoxide or to a sulfone with oxidizing agents such as sodium periodate, m-chloroperbenzoic acid or Oxone® in an solvent such as dichloromethane, alcohol or water or their mixtures.

The compounds of the present invention may also be prepared from a variety of substituted natural and unnatural amino acids of formula D46. The preparation of many of these acids is described in US Patent No. 5,206,237. The preparation of these intermediates in racemic form is accomplished by classical methods familiar to those skilled in the art (Williams, R. M. "Synthesis of Optically Active α -Amino Acids" Pergamon Press: Oxford, 1989; Vol. 7). Several methods exist to resolve (DL)-



D46

amino acids. One of the common methods is to resolve amino or carboxyl protected intermediates by crystallization of salts derived from optically active acids or amines. Alternatively, the amino group of carboxyl protected intermediates may be coupled to optically active acids by using chemistry described earlier. Separation of the individual diastereomers either by chromatographic techniques or by crystallization followed by hydrolysis of the chiral amide furnishes resolved amino acids. Similarly, amino protected intermediates may be converted to a

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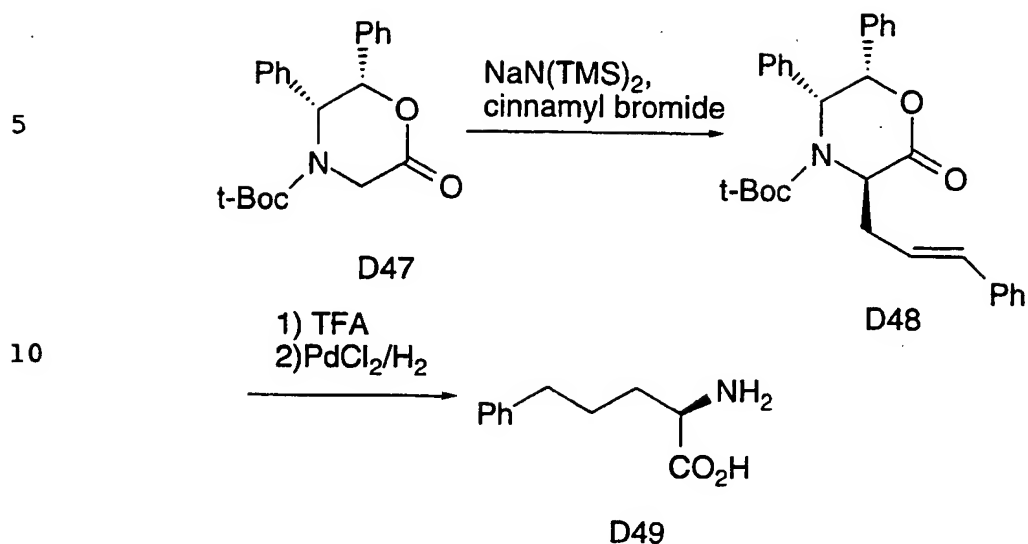
5 mixture of chiral diastereomeric esters and amides. Separation of the mixture using methods described above and hydrolysis of the individual diastereomers provides (D) and (L) amino acids. Finally, an enzymatic method to resolve N-acetyl derivatives of (DL)-amino acids has been reported by Whitesides and coworkers in *J. Am. Chem. Soc.* 1989, 111, 6354-6364.

When it is desirable to synthesize these intermediates in optically pure form, established methods include: (1) asymmetric electrophilic amination of chiral enolates (*J. Am. Chem. Soc.* 1986, 108, 6394-6395, 6395-6397, and 6397-6399), (2) asymmetric nucleophilic amination of optically active carbonyl derivatives, (*J. Am. Chem. Soc.* 1992, 114, 1906; *Tetrahedron Lett.* 1987, 28, 32), (3) diastereoselective alkylation of chiral glycine enolate synthons (*J. Am. Chem. Soc.* 1991, 113, 9276; *J. Org. Chem.* 1989, 54, 3916), (4) diastereoselective nucleophilic addition to a chiral electrophilic glycinate synthon (*J. Am. Chem. Soc.* 1986, 108, 1103), (5) asymmetric hydrogenation of prochiral dehydroamino acid derivatives ("*Asymmetric Synthesis, Chiral Catalysis*; Morrison, J. D., Ed; Academic Press: Orlando, FL, 1985; Vol 5), and (6) enzymatic syntheses (*Angew. Chem. Int. Ed. Engl.* 1978, 17, 176).

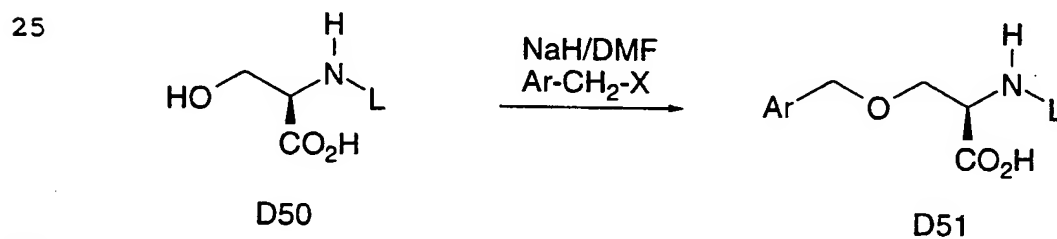
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SCHEME D14

For example, alkylation of the enolate of diphenyloxazinone D47 (*J. Am. Chem. Soc.* 1991, 113, 9276) with cinnamyl bromide in the presence of sodium bis(trimethylsilyl)amide proceeds smoothly to afford D48 which is converted into the desired (D)-2-amino-5-phenylpentanoic acid D49 by removing the N-t-butyloxycarbonyl group with trifluoroacetic acid and hydrogenation over a PdCl_2 catalyst (Scheme D14).

SCHEME D15

Intermediates of formula D46 which are O-benzyl-(D)-serine derivatives D51 are conveniently prepared from suitably substituted benzyl halides and N-protected-(D)-serine D50. The protecting group L is conveniently a BOC or a CBZ group. Benzylation of D64 can be achieved by a number of methods well known in the

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literature including deprotonation with two equivalents of sodium hydride in an inert solvent such as DMF followed by treatment with one equivalent of a variety of benzyl halides (*Synthesis* 1989, 36) as shown in Scheme D15.

5 The O-alkyl-(D)-serine derivatives may also be prepared using an alkylation protocol. Other methods that could be utilized to prepare (D)-serine derivatives of formula D51 include the acid catalyzed benzylation of carboxyl protected intermediates derived from D50 with reagents of formula $\text{ArCH}_2\text{OC}(=\text{NH})\text{CCl}_3$ (O. Yonemitsu *et al.*, *Chem.*
10 *Pharm. Bull.* 1988, 36, 4244). Alternatively, alkylation of the chiral glycine enolates (*J. Am. Chem. Soc.* 1991, *113*, 9276; *J. Org. Chem.* 1989, *54*, 3916) with $\text{ArCH}_2\text{OCH}_2\text{X}$ where X is a leaving group affords D51. In addition D,L-O-aryl(alkyl)serines may be prepared and resolved by methods described above.

15 It is noted that in some situations the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

 The utility of the compounds of the present invention as growth hormone secretagogues may be demonstrated by methodology known in the art, such as an assay described by Smith, *et al.*, *Science*,
20 260, 1640-1643 (1993) (see text of Figure 2 therein). In particular, all of the compounds prepared in the following examples had activity as growth hormone secretagogues in the aforementioned assay. Such a result is indicative of the intrinsic activity of the present compounds as
25 growth hormone secretagogues.

 The growth hormone releasing compounds of Formula I are useful *in vitro* as unique tools for understanding how growth hormone secretion is regulated at the pituitary level. This includes use in the evaluation of many factors thought or known to influence
30 growth hormone secretion such as age, sex, nutritional factors, glucose, amino acids, fatty acids, as well as fasting and non-fasting states. In addition, the compounds of this invention can be used in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that

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somatostatin inhibits growth hormone release. Other hormones that are important and in need of study as to their effect on growth hormone release include the gonadal hormones, e.g., testosterone, estradiol, and progesterone; the adrenal hormones, e.g., cortisol and other corticoids, epinephrine and norepinephrine; the pancreatic and gastrointestinal hormones, e.g., insulin, glucagon, gastrin, secretin; the vasoactive peptides, e.g., bombesin, the neurokinins; and the thyroid hormones, e.g., thyroxine and triiodothyronine. The compounds of Formula I can also be employed to investigate the possible negative or positive feedback effects of some of the pituitary hormones, e.g., growth hormone and endorphin peptides, on the pituitary to modify growth hormone release. Of particular scientific importance is the use of these compounds to elucidate the subcellular mechanisms mediating the release of growth hormone.

The compounds of Formula I may be administered to animals, including man, to release growth hormone *in vivo*. For example, the compounds can be administered to commercially important animals such as swine, cattle, sheep and the like to accelerate and increase their rate and extent of growth, to improve feed efficiency and to increase milk production in such animals. In addition, these compounds can be administered to humans *in vivo* as a diagnostic tool to directly determine whether the pituitary is capable of releasing growth hormone. For example, the compounds of Formula I can be administered *in vivo* to children. Serum samples taken before and after such administration can be assayed for growth hormone. Comparison of the amounts of growth hormone in each of these samples would be a means for directly determining the ability of the patient's pituitary to release growth hormone.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula I in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise an anabolic agent in addition to at least one of the compounds of Formula

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I or another composition which exhibits a different activity, e.g., an antibiotic growth permittant or an agent to treat osteoporosis or in combination with a corticosteroid to minimize the catabolic side effects or with other pharmaceutically active materials wherein the
5 combination enhances efficacy and minimizes side effects.

Growth promoting and anabolic agents include, but are not limited to TRH, diethylstilbesterol, estrogens, β -agonists, theophylline, anabolic steroids, enkephalins, E series prostaglandins, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and
10 compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Patent No. 4,411,890.

A still further use of the growth hormone secretagogues of this invention is in combination with other growth hormone secretagogues such as the growth hormone releasing peptides GHRP-6, GHRP-1 as described in U.S. Patent Nos. 4,411,890 and
15 publications WO 89/07110, WO 89/07111 and B-HT920 as well as hexarelin and the newly discovered GHRP-2 as described in WO 93/04081 or growth hormone releasing hormone (GHRH, also designated GRF) and its analogs or growth hormone and its analogs or
20 somatomedins including IGF-1 and IGF-2 or α -adrenergic agonists such as clonidine or serotonin 5HT_{1D} agonists such as sumatriptan or agents which inhibit somatostatin or its release such as physostigmine and pyridostigmine.

As is well known to those skilled in the art, the known and
25 potential uses of growth hormone are varied and multitudinous. The administration of the compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself. These varied uses of the present compounds thus may be summarized as follows: stimulating growth
30 hormone release in elderly humans; treating growth hormone deficient adults; prevention of catabolic side effects of glucocorticoids; treatment of osteoporosis; stimulation of the immune system, acceleration of wound healing; accelerating bone fracture repair; treatment of growth retardation; treating acute or chronic renal failure or insufficiency;

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treatment of physiological short stature, including growth hormone deficient children; treating short stature associated with chronic illness; treatment of obesity and growth retardation associated with obesity; treating growth retardation associated with Prader-Willi syndrome and
5 Turner's syndrome; accelerating the recovery and reducing hospitalization of burn patients or following major surgery such as gastrointestinal surgery; treatment of intrauterine growth retardation, and skeletal dysplasia, treatment of peripheral neuropathies; replacement of growth hormone in stressed patients; treatment of osteochondro-
10 dysplasias, Noonans syndrome, schizophrenia, depression, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treatment of pulmonary dysfunction and ventilator dependency; attenuation of protein catabolic response after a major operation; treating malabsorption syndromes; reducing cachexia and protein loss due to chronic illness such
15 as cancer or AIDS; accelerating weight gain and protein accretion in patients on TPN (total parenteral nutrition); treatment of hyperinsulinemia including nesidioblastosis; adjuvant treatment for ovulation induction and to prevent and treat gastric and duodenal ulcers; to stimulate thymic development and prevent the age-related decline of
20 thymic function; adjunctive therapy for patients on chronic hemodialysis; treatment of immunosuppressed patients and to enhance antibody response following vaccination; increasing the total lymphocyte count of a human, in particular, increasing the T4/T8-cell ratio in a human with a depressed T4/T8-cell ratio resulting, for example, from physical trauma,
25 such as closed head injury, or from infection, such as bacterial or viral infection, especially infection with the human immunodeficiency virus; improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; stimulation of osteoblasts, bone remodelling, and cartilage growth; stimulation of the
30 immune system in companion animals and treatment of disorders of aging in companion animals; growth promotant in livestock; and stimulation of wool growth in sheep. Further, the instant compounds are useful for increasing feed efficiency, promoting growth, increasing milk production and improving the carcass quality of livestock.

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In particular, the instant compounds are useful in the prevention or treatment of a condition selected from the group consisting of: osteoporosis; catabolic illness; immune deficiency, including that in individuals with a depressed T4/T8 cell ratio; hip fracture;
5 musculoskeletal impairment in the elderly; growth hormone deficiency in adults or in children; obesity; cachexia and protein loss due to chronic illness such as AIDS or cancer; and treating patients recovering from major surgery, wounds or burns, in a patient in need thereof.

It will be known to those skilled in the art that there are
10 numerous compounds now being used in an effort to treat the diseases or therapeutic indications enumerated above. Combinations of these therapeutic agents some of which have also been mentioned above with the growth hormone secretagogues of this invention will bring additional, complementary, and often synergistic properties to enhance the growth
15 promotant, anabolic and desirable properties of these various therapeutic agents. In these combinations, the therapeutic agents and the growth hormone secretagogues of this invention may be independently present in dose ranges from one one-hundredth to one times the dose levels which are effective when these compounds and secretagogues are used singly.

20 Combined therapy to inhibit bone resorption, prevent osteoporosis and enhance the healing of bone fractures can be illustrated by combinations of bisphosphonates and the growth hormone secretagogues of this invention. The use of bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N.A.T., Role of
25 Bisphosphonates in Metabolic Bone Diseases, Trends in Endocrinol. Metab., 4, 19-25 (1993). Bisphosphonates with these utilities include alendronate, tiludronate, dimethyl-APD, risedronate, etidronate, YM-175, clodronate, pamidronate, and BM-210995. According to their potency, oral daily dosage levels of the bisphosphonate of between 0.1 mg and 5 g
30 and daily dosage levels of the growth hormone secretagogues of this invention of between 0.01 mg/kg to 20 mg/kg of body weight are administered to patients to obtain effective treatment of osteoporosis.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or

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subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated in dosage forms appropriate for each route of administration.

5 Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the
10 case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions,
15 syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Preparations according to this invention for parenteral
20 administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants
25 such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile
30 solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

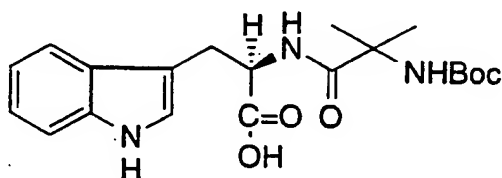
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Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

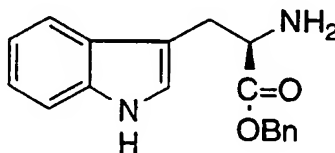
The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 100 mg/kg. of body weight daily are administered to patients and animals, e.g., mammals, to obtain effective release of growth hormone.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention. As will be apparent, the examples and intermediates designated "A" correspond to the compounds of the first embodiment, those designated "B" correspond to the compounds of the second embodiment, and those designated "C" correspond to the compounds of the third embodiment.

INTERMEDIATE 1



Step A:



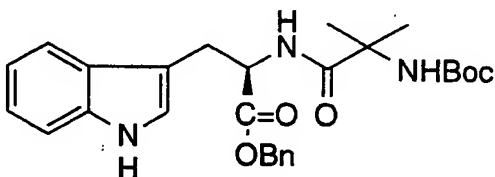
To a solution of the commercially available N-t-BOC-D-tryptophan (25.0 g, 82.2 mmol), benzyl alcohol (10.2 mL, 98.6 mmol), and DMAP (100 mg) in dichloromethane (200 mL) at 0°C, was added EDC (17.4 g, 90.4 mmol) in several portions over a one hour period. The

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reaction mixture was stirred at room temperature for six hours and was poured into water (200 mL), and the organic layer was separated. The organic solution was washed with a mixture of brine and 3 N hydrochloric acid, dried over anhydrous magnesium sulfate, filtered and concentrated to give a thick oil, which solidified upon standing.

To a solution of this oil in 30 mL of dichloromethane was added 20 mL of TFA and stirred for 1h. The reaction mixture was concentrated, neutralized carefully with saturated aqueous sodium bicarbonate solution, and extracted with dichloromethane (2X100 mL). The combined organic solution was washed with brine (100 mL), passed through a short column of silica gel eluting with 5-10% methanol in dichloromethane to give 23.2 g of the amine as an oil after evaporation.

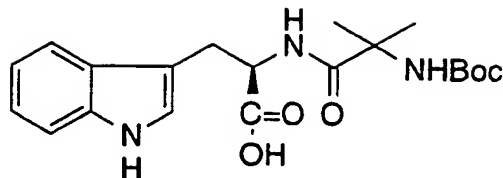
Step B:



To a solution of the above product, HOBT (10.6 g, 78.8 mmol) and N-BOC- α -methyl alanine (19g, 94.5 mmol) in 200 mL of dichloromethane, was added EDC (19.5 g, 0.102 mol) in several portions at 0°C. After 5 minutes, the clear reaction mixture became milky. After stirring at room temperature overnight, the reaction mixture was poured into 200 mL of water and the organic layer was separated. The organic solution was washed with brine, and with a brine and saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered and concentrated to give a thick oil, which was purified by flash chromatography eluting with a gradient of 10-40% ethyl acetate in hexane to give the desired material (28.7 g).

^1H NMR (CDCl_3 , 200 MHz) δ 8.48 (br.s, 1H), 7.54 (br.d, 1H), 7.38-7.23 (m, 3H), 7.19 (br.d, 2H), 7.15-7.00 (m, 1H), 6.90 (d, 1H), 6.86 (d, 1H), 5.06 (br.s, 2H), 4.95 (ddd, 1H), 3.30 (2dd, 2H), 1.40 (s, 15H)

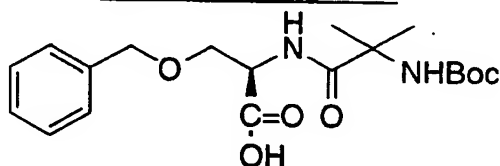
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Step C:

A solution of the material from Step B (28.7g) in 200 mL of ethanol was stirred at RT under a H₂ balloon for 20 minutes in the presence of 10% palladium on carbon (2 g). The catalyst was filtered off through a pad of celite and washed with ethyl acetate. The filtrate was concentrated to give the acid as a slightly pink foam (23.3 g).

¹H NMR (CD₃OD, 400 MHz) δ 7.56 (d, J=8 Hz, 1 H), 7.31 (dd, J=1, 8 Hz, 1 H), 7.09 (s, 1 H), 7.07 (dt, J=1, 7 Hz, 1 H), 6.98 (dt, J=1, 7 Hz, 1 H), 4.69 (t, J=6 Hz, 1 H), 3.34-3.23 (m, 2 H), 1.35 (s, 3 H), 1.34 (s, 9 H), 1.29 (s, 3 H).

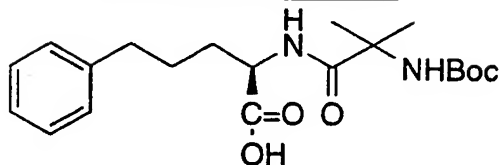
FAB-MS calc. for C₂₀H₂₇N₃O₅ : 389 ; Found 390 (M+H), 290 (M+H-100 (BOC)).

INTERMEDIATE 2

Following the procedures for the preparation of Intermediate 1 using N-t-Boc-O-Benzyl-D-serine in the place of N-t-BOC-D-tryptophan gave Intermediate 2.

FAB-MS calc. for C₁₉H₂₈N₂O₆ : 380 ; Found 381 (M+H), 325 (M+H-56 (t-Bu)), 281 (M+H-100 (BOC)).

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INTERMEDIATE 3

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Step A: (DL)-N-acetyl-2-amino-5-phenylpentanoic acid

To a solution of sodium (2.3 g, 0.1 mol) in ethanol (60 mL) under nitrogen at room temperature, was added diethyl acetamidomalonate. The mixture was stirred at room temperature for one hour, and then 1-bromo-3-phenylpropane was added dropwisely. After the addition, the mixture was stirred at room temperature for two hours, then refluxed overnight. It was cooled to room temperature and partitioned between water and ethyl acetate. The organic layer was washed with sodium bicarbonate in water, dried over MgSO₄ and evaporated to give an intermediate (32.5 g, 97%).

¹H NMR (CDCl₃, 400MHz) 7.26-7.10 (m, 5 H); 6.75 (br. s, 1 H); 4.19 (q, J=7 Hz, 4 H); 2.58 (t, J=7.9 Hz, 2 H); 2.39-2.35 (m, 2 H); 2.00 (s, 3 H); 1.43-1.39 (m, 2 H); 1.20 (t, J=7 Hz, 6 H).

The product above was suspended in 190 mL of 2.5 N NaOH in water and refluxed for two hours. The mixture was cooled to 0°C, and it was carefully neutralized with 6 N HCl to pH2. The precipitate was collected using a sintered glass funnel and washed with a small amount of cold water and air dried. The solid was then suspended in 300 mL of water and refluxed for four hours. The solution was cooled and acidified to pH1 and the solid was collected by filtration (15.3 g, 67%).

¹H NMR (CD₃OD, 400MHz) 7.26-7.12 (m, 5 H); 4.90-4.37 (m, 1 H); 2.65-2.60 (m, 2 H); 1.97 (s, 3 H); 1.87 -1.82 (m, 1 H); 1.73-1.65 (m, 3 H).

Step B: (D)-N-acetyl-2-amino-5-phenylpentanoic acid

The racemic intermediate from the previous step (10 g, 42.5 mmol) and CoCl₃·6H₂O were dissolved in 21 ml of 2 N KOH and 200 mL of water at 40°C, and the pH of the solution was adjusted to 8 by the addition of the several drops of 2 N KOH. Then acylase I (*Aspergillus* sp, 0.5 u/mg, from Sigma; 0.9 g) was added with vigorous stirring. The

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reaction mixture was stirred for one day at 40°C and the pH was kept at 8 by the addition of a few drops of KOH. The solid which formed was filtered off. The filtrate was acidified by 3 N HCl to pH2, and was extracted with ethyl acetate (200 mLX4). The organic extracts were

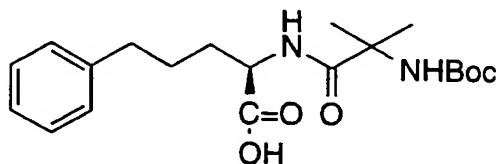
combined and evaporated to give a white solid (4.64 g, 46%)
¹H NMR (CD₃OD, 400MHz) 7.26-7.12 (m, 5 H); 4.90-4.37 (m, 1 H); 2.65-2.60 (m, 2 H); 1.97 (s, 3 H); 1.87 -1.82 (m, 1 H); 1.73-1.65 (m, 3 H).

Step C: (D)-N-t-Boc-2-amino-5-phenylpentanoic acid

The intermediate from step B (4.2 g, 17.8 mmol) was suspended in 2 N HCl (100 mL) and refluxed for two hours. The reaction mixture was evaporated in vacuo to remove water and hydrochloric acid to yield a white solid. To a solution of this solid in 50 mL of water, was added 3 N NaOH until the pH 11, then di-t-butyl dicarbonate (4.66 g, 21.4 mmol) was added with vigorous stirring. After four hours, the reaction mixture was acidified to pH2 with 3 N HCl and it was extracted with ethyl acetate (100 mLX3). The organic extracts were combined and evaporated to give a white solid (6.56 g, crude) which was used without purification.

¹H NMR (CD₃OD, 400MHz) 7.26-7.12 (m, 5 H); 4.11-4.08 (m, 1 H); 2.65-2.60 (m, 2 H); 1.83-1.62 (m, 4 H); 1.43 (s, 9 H).

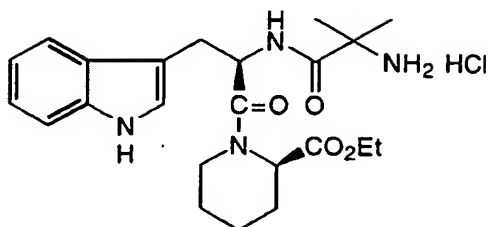
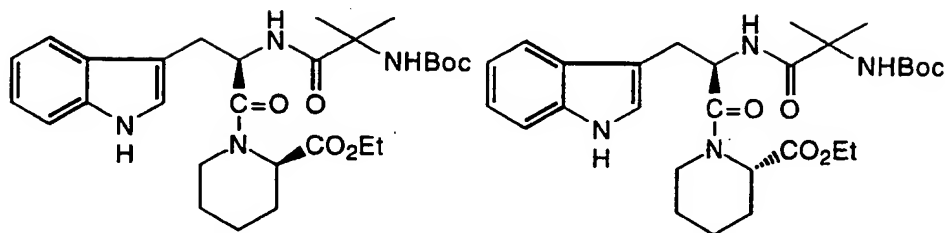
Step D:



Following the procedures for the preparation of Intermediate 1 using (D)-N-t-Boc-2-amino-5-phenylpentanoic acid in the place of N-t-BOC-D-tryptophan gave Intermediate 3.

¹H NMR (CDCl₃, 400MHz) 7.24-7.20 (m, 2H), 7.15-7.04 (m, 3H), 4.60-4.55 (m, 1H), 2.62-2.55 (m, 2H), 2.00-1.86 (m, 1H), 1.78-1.60 (m, 3H), 1.50 (s, 6H), 1.30 (s, 9H).

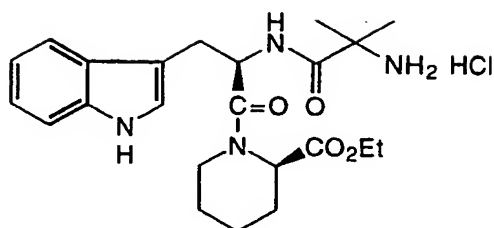
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EXAMPLE A1Step A:

To a solution of ethyl (dl) pipecolate (1 g), HOBT (860 mg) and Intermediate 1 (2.47 g) in dichloromethane (80 mL) at 0°C, was added EDC (2.3 g). The reaction mixture was stirred at room temperature overnight. The solution was washed with water, saturated sodium bicarbonate solution, and saturated sodium chloride solution, dried over anhydrous magnesium sulfate; then filtered and concentrated to give a crude product. The crude product was purified by MPLC eluting with 60% ethyl acetate in hexane to give the product as a mixture of two diastereomers (2.79 g). Separation of 500 mg of the mixture by MPLC eluting with 50% ethyl acetate in hexane yielded the two individual diastereomers. The diastereomer which came out of the column first was designated as d1 (187 mg) and the stereochemistry of the pipecolinic acid ester was subsequently shown to be R. The one which came out last was designated as d2 (116 mg) and the stereochemistry of the pipecolinic acid ester in it is S. In addition, there were mixed fractions which were combined and evaporated to yield 190 mg of a mixture of d1 and d2.

d1: FAB-MS calc. for C₂₈H₄₀N₄O₆: 528 ; Found: 529 (M+H)
d2: FAB-MS calc. for C₂₈H₄₀N₄O₆: 528 ; Found: 529 (M+H)

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Step B:

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A solution of the compound d1 from Step A (140 mg) in ethyl acetate (5 mL) was cooled to 0°C. While stirring, hydrogen chloride gas was bubbled into the mixture until saturation occurred. The reaction was stirred for 15 minutes. The solution was then concentrated to remove ethyl acetate. The residue was then redissolved in dichloromethane and hexane followed by evaporation in vacuo to afford the product as a solid (110 mg).

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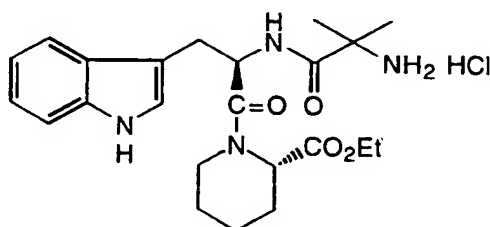
FAB-MS calc. for C₂₃H₃₂N₄O₄: 428 ; Found: 429 (M+H)

¹HNMR (400 MHz, CD₃OD): compound exists as a mixture of rotamers (about 2:1). 7.57 (d, 1 H), 7.36 & 7.32 (2 d, 1 H), 7.14-7.00 (m, 3 H), 5.30-5.20 (m), 5.17-5.13 (m), 4.36 (d), 4.21 (q, J=7 Hz), 4.13 (q, J=7 Hz), 4.00 (md), 3.35-3.04 (m), 2.60 (dt), 3.30 (br. d), 2.70 -2.50 (m), 1.57 (s), 1.55 (s), 1.52 (s), 1.50-1.20 (m), 1.33 (s), 1.27 (t, J=7 Hz), 1.21 (t, J=7 Hz), 1.15-1.10 (m), 0.75-0.65 (m), 0.30-0.20 (m).

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EXAMPLE A2

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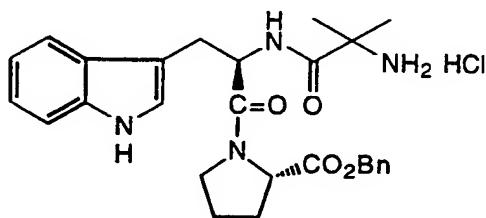
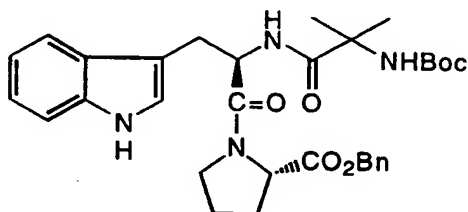


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Prepared by the procedure described in Example A1, Step B from the intermediate d2 from Example A1, step A (40 mg) and HCl gas at 0°C in ethyl acetate (3 mL). Product: 28 mg.
FAB-MS calc. for C₂₃H₃₂N₄O₄: 428 ; Found: 429 (M+H)

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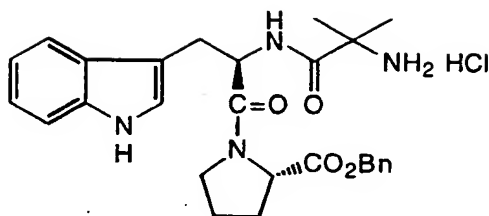
¹HNMR (400 MHz, CD₃OD): compound exists as a mixture of rotamers (about 5:1). 7.56 (d, J= 8 Hz 5/6 H), 7.50 (d, 1/6 H), 7.34 (d, J=8 Hz, 5/6 H), 7.31 (d, 1/6 H), 7.12-7.00 (m, 3 H), 5.28 (dd, 5/6 H), 5.15-5.11 (m, 1/6 H), 5.11-5.07 (m, 1/6 H), 5.02-4.98 (m, 5/6 H), 4.52-4.45 (m), 4.12 (q, J=7 Hz), 4.25-4.00 (m), 3.65 (m), 3.30-3.05(m), 2.80-2.70 (m), 2.32-2.25 (m), 2.02-1.97 (m), 1.75-1.65 (m), 1.57 (s), 1.52 (s), 1.51 (s), 1.40-0.85 (m), 1.22 (t, J= 7 Hz), 0.41-0.30 (m).

EXAMPLE A3Step A:

To a stirred solution of L-proline benzyl ester hydrochloride (155 mg, 0.64 mmole), Intermediate 1 (250 mg, 0.64 mmole), HOBT (1 eq.), and NMM (0.07 mL, 0.64 mmole) in dichloromethane at 0°, was added EDC (246 mg, 1.28 mmole). The reaction mixture was stirred at 0° overnight, and then partitioned between 3 N HCl and ethyl acetate. The organic layer was washed with brine and saturated sodium bicarbonate and dried and evaporated. MPLC purification eluting with 50% ethyl acetate gave the intermediate tripeptide benzyl ester (338 mg, 91.5%).

FAB-MS calc. for C₃₂H₄₀N₄O₆: 576 ; Found: 577 (M+H)

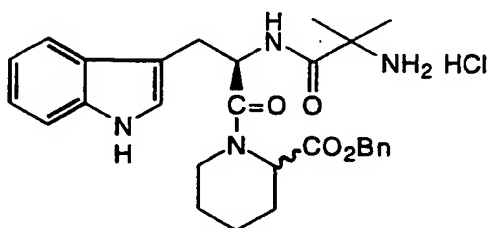
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Step B:

Prepared by the procedure described in Example A1, Step B from the intermediate from the previous step (280 mg) and HCl gas in ethyl acetate (10 mL) at 0°C. Reaction time: 25 minutes. Product: 218 mg.

FAB-MS calc. for C₂₇H₃₂N₄O₄: 476; Found: 477 (M+H)

¹HNMR (400 MHz, CD₃OD): 8.20 (d), 7.54 (d, J=7.9 Hz, 1H), 7.34-7.00 (m, 9H), 5.11 (dd, J=4.2 Hz, 16.5 Hz, 2H), 4.99-4.94 (m, 1H), 4.23-4.20 (m, 1H), 3.58-3.53 (m, 1H), 3.31-3.13 (m, 2H), 2.77-2.75 (m, 1H), 1.71-1.60 (m, 3H), 1.55 (s, 3H), 1.51 (s, 3H), 1.37-1.33 (m, 1H).

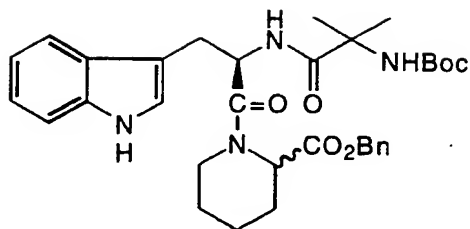
EXAMPLE A4Step A: (dl)-Pipicolinic acid, benzyl ester

A solution of (dl)-pipicolinic acid (25g), p-toluenesulfonic acid (38g), and benzyl alcohol (84g) in toluene (200 mL) was refluxed under azeotropic conditions for one day. The solution was cooled to room temperature and the resulting crystals were collected to give the desired product (52.4 g). The product was washed with 3 N NaOH to remove toluenesulfonic acid, and then reacted with HCl gas in ethyl acetate to convert it to the hydrochloride salt.

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Step B:

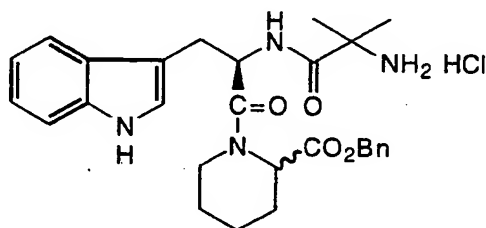
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Prepared by the procedure described in Example A3, Step A
 10 from (dl)-pipecolinic acid benzyl ester hydrochloride (3.5 g).
 Intermediate 1 (5.00 g), HOBT (1.74 g), NMM (1.42 mL) and EDC (3.94
 g). Product: 6.32 g
 FAB-MS calc. for C₃₃H₄₂N₄O₆: 590 ; Found: 591 (M+H)

15 Step C:

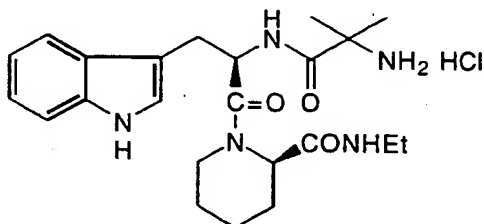
20



Prepared by the procedure described in Example A1, Step B
 from the intermediate from the previous step (250 mg) and HCl gas in
 ethyl acetate at 0°C to give the title compound (211 mg)
 25 FAB-MS calc. for C₂₈H₃₄N₄O₄: 490 ; Found: 491 (M+H)

EXAMPLE A5

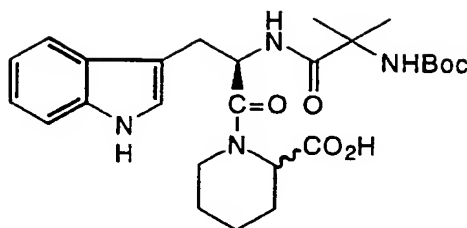
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Step A:

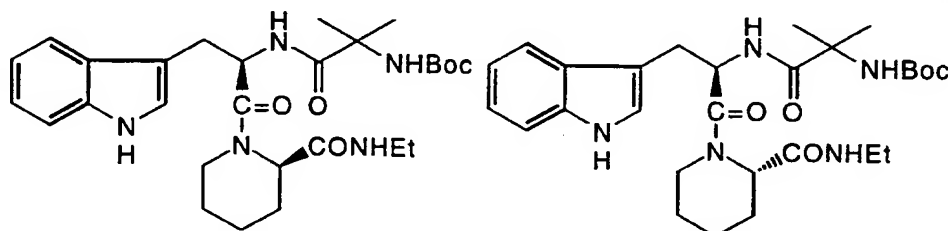
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10 A suspension of the product from Example A4, step B (5.30 g) and 10% palladium on carbon (270 mg) in ethanol (100 mL) was stirred under a hydrogen balloon for 3 hours. The reaction mixture was filtered through celite, evaporated to give the acid (4.48g).

Step B:

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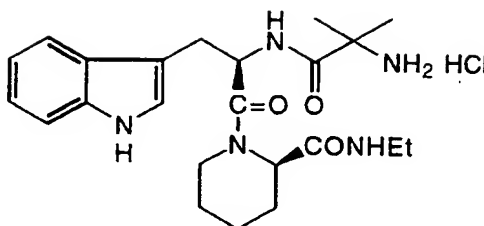
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25 Prepared similarly by the procedure described in Example A3, Step A from the acid intermediate from the previous step (200 mg), ethyl amine hydrochloride (27 mg), HOBt (54 mg), NMM (0.07 mL), and EDC (154 mg) to give a mixture of two diastereomers, which were separated by MPLC eluting with ethyl acetate. The isomer which came out of the column first was designated as d1 (76 mg) , and the isomer which came out second as d2 (165 mg).

d1 FAB-MS calc. for C₂₈H₄₁N₅O₅: 527 ; Found: 528 (M+H)

30 d2 FAB-MS calc. for C₂₈H₄₁N₅O₅: 527 ; Found: 528 (M+H)

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Step C:

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Prepared similarly by the procedure described in Example A1, Step B from intermediate from the previous step (d1) (60 mg) and HCl gas in ethyl acetate (5 mL) at 0°C to give the title compound (38 mg). Reaction time: 20 minutes.

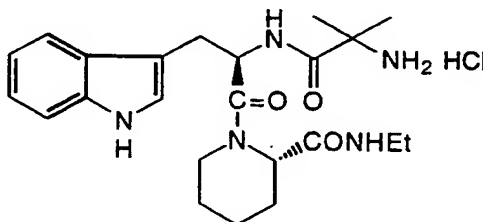
10

FAB-MS calc. for C₂₃H₃₃N₅O₃: 427 ; Found: 428 (M+H)

¹HNMR (400 MHz, CD₃OD): δ 7.63 - 7.00 (m, 5 H), 5.33 (t), 5.40 - 5.25 (m), 5.11 - 5.09 (m), 4.32 (br. d), 4.16 - 4.12 (m), 4.00 (md), 3.35 - 3.03 (m), 2.96 (q, J = 7 Hz), 2.30 (dt), 2.19 (br. d), 1.95 - 1.40 (m), 1.66 (s), 1.64 (s), 1.40 - 1.20 (m), 1.20 - 1.00 (m), 1.12 (t, J = 7 Hz), 1.03 (t, J = 7 Hz), 0.65 - 0.52 (m), -0.44 - -0.53 (m).

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EXAMPLE A6

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Prepared similarly by the procedure described in Example A1, Step B from intermediate in Example A5 step B (d2) (100 mg) and HCl gas in ethyl acetate (5 mL) at 0°C to give the title compound (78 mg). Reaction time: 20 minutes.

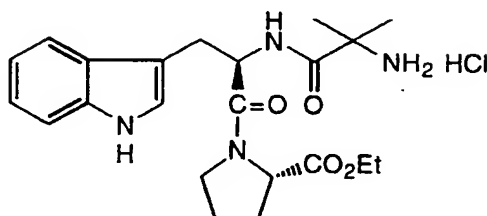
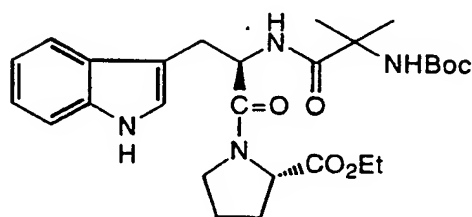
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FAB-MS calc. for C₂₃H₃₃N₅O₃: 427 ; Found: 428 (M+H)

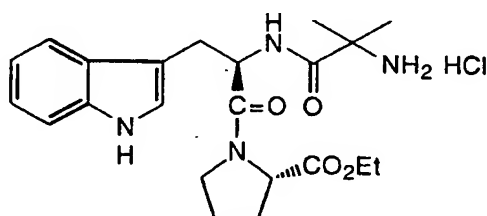
¹HNMR (400 MHz, CD₃OD): δ 7.54 (d, J = 8 Hz, 1 H), 7.35 (d, J = 8 Hz, 1 H), 7.16 (s, 1 H), 7.13 - 7.00 (m, 2 H), 4.98 (dd, J = 6 Hz, 10 Hz), 4.93 (d, 4 Hz), 3.53 (br. d, J = 12 Hz, 1 H), 3.35 - 3.22 (m), 3.14 - 3.09 (m, 1 H), 2.85 (dt, J = 3, 13 Hz, 1 H), 2.02 (br. d, J = 12 Hz), 1.65 (s, 3

- 116 -

H), 1.61 (s, 3 H), 1.10 (t, 7 Hz, 3 H), 1.05- 0.92 (m, 2 H), 0.72- 0.62 (m, 1 H), -0.25 - -0.30 (m, 1 H).

EXAMPLE A7Step A:

Prepared by the procedure described in Example A3, Step A from L-proline ethyl ester hydrochloride (115 mg, 0.642 mmole), Intermediate 1 (250 mg, 0.642 mmole), HOBT (1 eq.), NMM(0.07 mL, 0.642 mmole), and EDC (246 mg, 1.28 mmole). Product: 330 mg FAB-MS calc. for C₂₇H₄₀N₄O₆: 514 ; Found: 515 (M+H)

Step B:

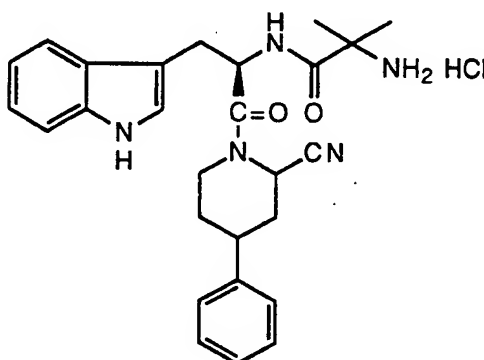
Prepared by the procedure described in Example A1, Step B from the intermediate from the previous step (280 mg) and HCl gas in ethyl acetate (10 mL) at 0°C. Reaction time: 25 minutes. Product: 220 mg.

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FAB-MS calc. for C₂₂H₃₂N₄O₄: 414; Found: 415 (M+H)

¹HNMR (400 MHz, CD₃OD): 7.53 (d, J=7.9 Hz, 1H), 7.34 (d, J=8.1 Hz, 1H), 7.14-7.01 (m, 3H), 4.97-4.84 (m, 1H), 4.15-4.06 (m, 3H), 3.60-3.53 (m, 1H), 3.31-3.13 (m, 2H), 2.77-2.72 (m, 1H), 1.72-1.59 (m, 3H), 1.57 (s, 3H), 1.50 (s, 3H), 1.36-1.27 (m, 1H), 1.23 (t, J=7.1 Hz, 3H).

EXAMPLE A8



Step A: 2-Cyano-1-hydroxy-4-phenylpiperidine

To a stirred solution of 4-phenylpiperidine (10 g, 0.062 mole) in methanol (30 mL), was added a solution of sodium tungstate dihydrate (0.82 g, 2.48 mmole) in water (7 mL). With stirring at 0°, hydrogen peroxide (30%, 13.9 mL, 0.136 mole) was added dropwise. After complete addition, the reaction mixture was stirred for an additional 3 hours, and then sodium cyanide (4.56 g, 0.093 mole) was added, followed by 4 N HCl (22 mL, 0.088 mole). The reaction mixture was stirred overnight during which time it warmed to room temperature. The solid was collected by filtration through glass sinter funnel, and the solution was neutralized to pH 7 and was extracted with dichloromethane. The organic extract was combined with the solid and dried over MgSO₄ and evaporated. Flash column purification eluting with 40% ethyl acetate in hexane gave 2-cyano-1-hydroxy-4-phenylpiperidine (8.6 g).

¹HNMR (400 MHz, CDCl₃): 7.35-7.17 (m, 5 H), 6.01 (br. s, 1H), 4.34 (br. s, 1 H), 3.31 (td, J=3, 11 Hz, 1 H), 3.09 (dt, J=11, 3 Hz, 1 H), 2.93-2.86 (m, 1H), 2.20-2.10 (m, 2 H), 1.97-1.80 (m, 2 H).

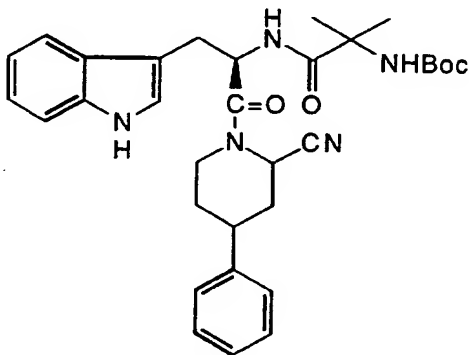
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Step B: 2-Cyano-4-phenylpiperidine

To a stirred solution of the intermediate from the previous step (500 mg) in methanol (10 mL) at room temperature, was added
5 TiCl₃ (10% solution in 20-30% hydrochloric acid (3 mL). The mixture was stirred for 15 minutes and was neutralized by addition of 3 N NaOH. The residue were extracted with dichloromethane four times and the organic extracts was combined, dried over MgSO₄, and evaporated to
10 give 450 mg of 2-cyano 4-phenylpiperidine, which was used without further purification.

Step C:

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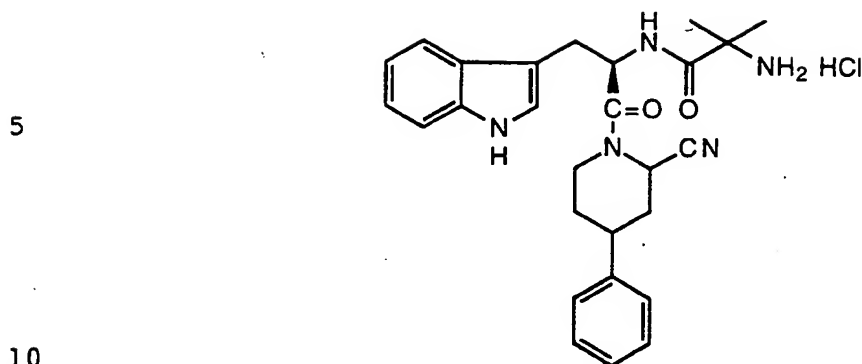
Following the procedure from Example A3, Step A, using the intermediate from the previous step, afforded two compounds after
25 MPLC purification eluting with 60% ethyl acetate in hexane. The one which came out of the column first was designated as diastereomer 1, and the other one as diastereomer 2.

d1: FAB-MS calc. for C₃₂H₃₉N₅O₄: 557 ; Found: 558 (M+H)

d2: FAB-MS calc. for C₃₂H₃₉N₅O₄: 557 ; Found: 558 (M+H)

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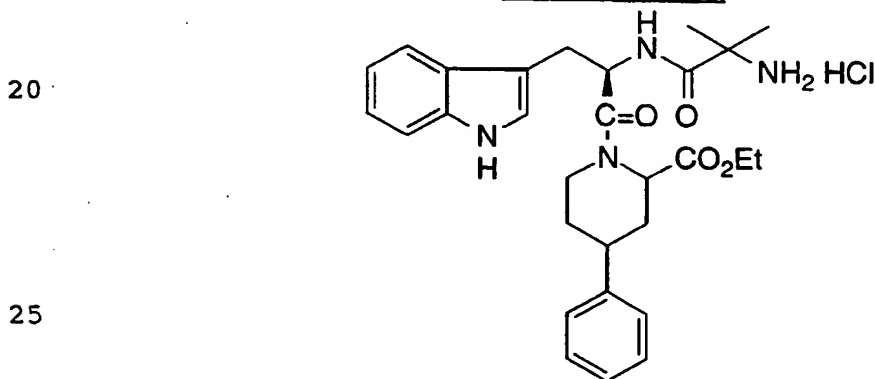
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Step D:

Following the experimental procedure from Example A1, Step B using products from the previous step and HCl gas in ethyl acetate at 0°C gave the desired products.

15 d1: FAB-MS calc. for C₂₇H₃₁N₅O₂: 457 ; Found: 458 (M+H)

d2: FAB-MS calc. for C₂₇H₃₁N₅O₂: 457 ; Found: 458 (M+H)

EXAMPLE A9Step A: 2-Cyano-4-phenylpyridine

To a stirred solution of 4-phenylpyridine N-oxide (25 g, 0.146 mmol) in dichloromethane (200 ml) at room temperature was added trimethylsilyl cyanide (17.4 g), followed by the slow addition of dimethyl carbamyl chloride (16.2 ml) in dichloromethane (50 ml) over a 30 minute period. The reaction mixture was stirred at room temperature for one day, and then to it potassium carbonate solution (10%, 150 ml) was added slowly. Stirring continued for an additional 30 minutes, the

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organic layer was separated, and the aqueous layer was extracted with dichloromethane. The extracts were combined and dried over magnesium sulfate. Evaporation in vacuo gave a crude reaction product (35 g) as a white solid. It was used without further purification.

5 FAB-MS calc. for C₁₂H₈N₂: 180 ; Found: 181 (M+H)
1HNMR (400 MHz, CD₃OD): 8.71 (dd, 1 H), 8.19 (dd, 1H), 7.94 (dd, 1 H), 7.81 -7.78 (m, 2 H), 7.56-7.50 (m, 3 H).

10 Step B: 4-Phenylpyridine-2-carboxylic acid

A solution of the product from the previous step (25 g) in 100 ml of 6N HCl was refluxed for one day. The solution was cooled to room temperature, at which time, crystallization started to occur. The crystals were filtered and collected to give the product (27.5 g, 87%).

15 Step C: Ethyl 4-phenylpyridine-2-carboxylate hydrochloride

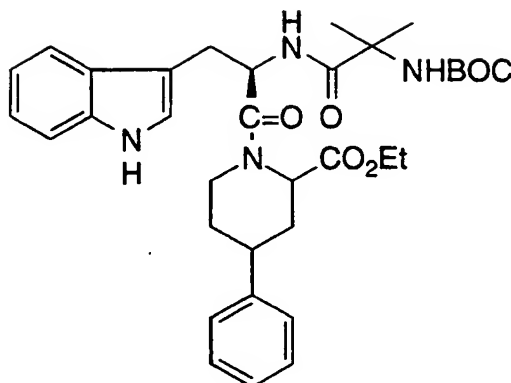
To a solution of the intermediate prepared in the previous step (5.0 g, 21.2 mmol), ethanol (2 g), DMAP (20 mg) and N-methyl morpholine (1 eq.) in dichloromethane, was added EDC (1.5 eq.). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium bicarbonate, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 40% ethyl acetate in hexane gave ethyl 4-phenylpyridine-2-carboxylate (3.71 g, 77%). The compound was converted to its HCl salt by treatment with HCl gas in ethyl acetate followed by evaporation.

25 Step D: Ethyl 4-phenylpiperidine-2-carboxylate

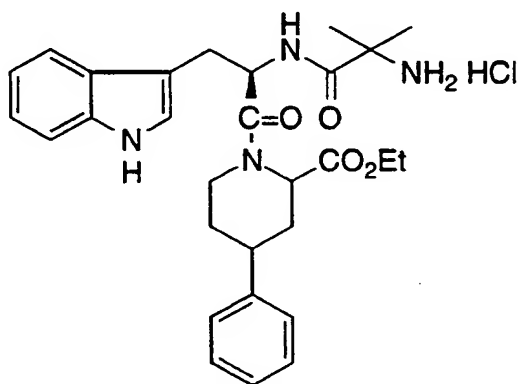
A suspension of the product from the previous step (200 mg) and platinum dioxide (20 mg) in ethanol was stirred under a hydrogen balloon for three hours. The reaction mixture was then filtered through celite and evaporated. The resulting material was used without further purification.

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Step E:

To a solution of the intermediate prepared in the previous step (200 mg), and Intermediate 1 (1 eq.), HOBT (1 eq.), and NMM (1 eq.) in dichloromethane was added EDC (1.5 eq.) at 0°C. The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered and then concentrated. Purification by MPLC eluting with 50% ethyl acetate in hexane provided the compound as a diastereomeric mixture.

Step F:

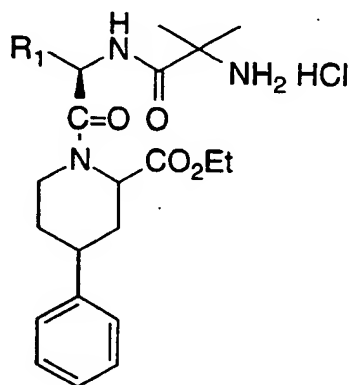
To a stirred solution of the intermediate from the previous step (30 mg) in ethyl acetate (2 mL) at 0°C, was bubbled HCl gas until it was saturated. The reaction mixture was stirred for 15 minutes and was evaporated to dryness to give the product.

FAB-MS calc. for C₂₉H₃₆N₄O₄: 504; Found 505 (M+H)

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The additional Products shown in Table AI were prepared according to Example A9 Steps E and F, using Intermediate 2 or Intermediate 3 and the intermediate from step D.

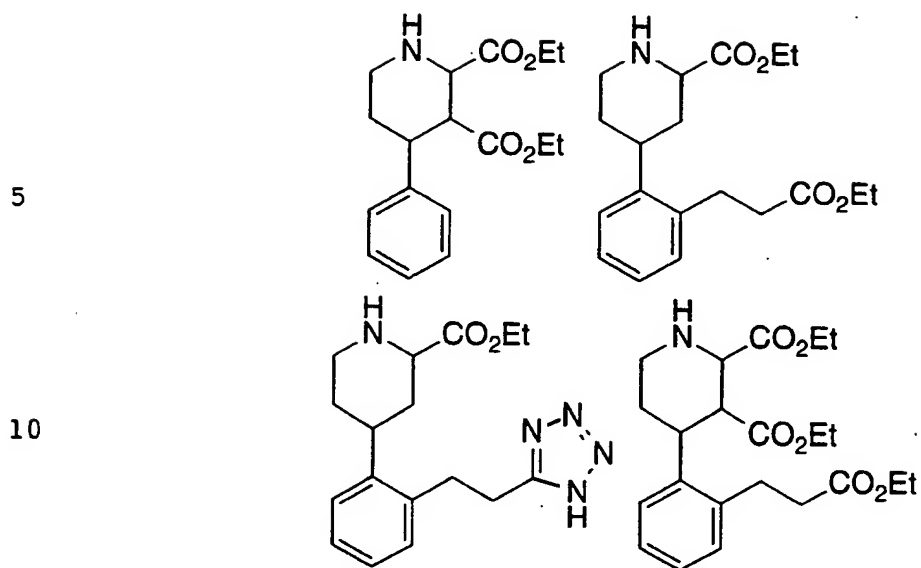
TABLE AI: ADDITIONAL EXAMPLES



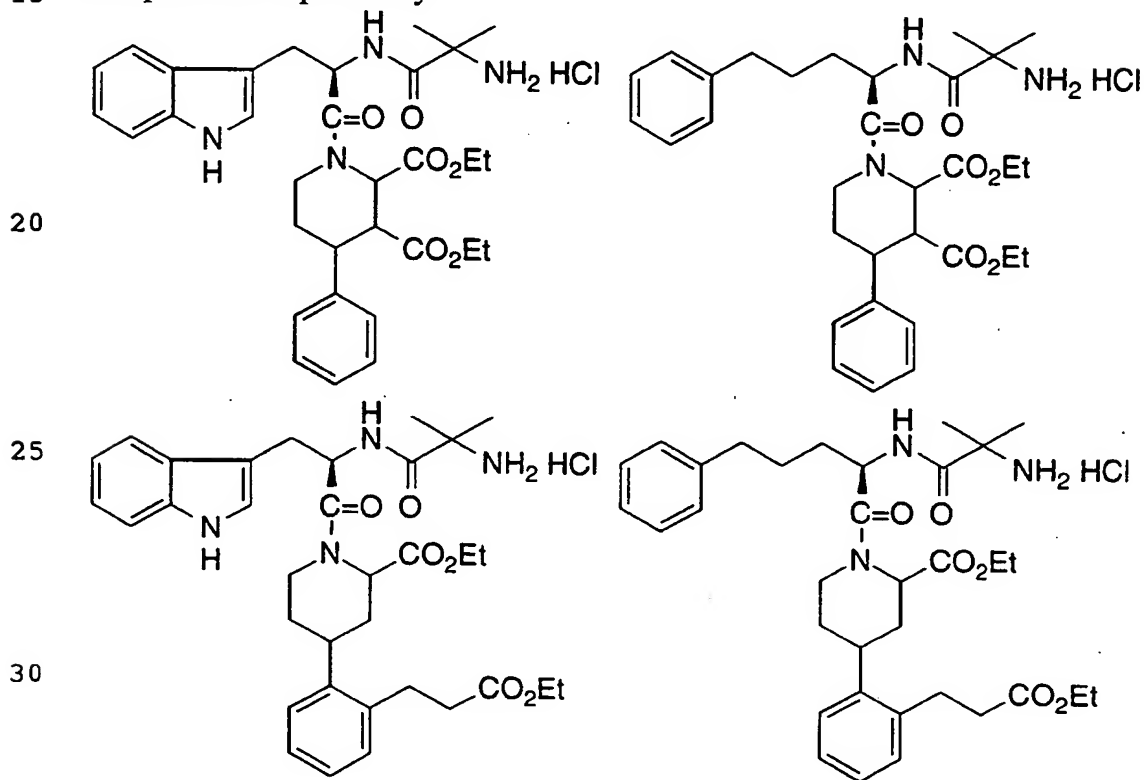
| | | Product |
|-------|--------------------------------------|--|
| entry | R1 | MF FAB-MS (M+1) |
| 1 | Ph(CH ₂) ₃ - | C ₂₉ H ₃₉ N ₃ O ₄ 494 |
| 2 | PhCH ₂ OCH ₂ - | C ₂₈ H ₃₇ N ₃ O ₅ 496 |

Likewise the compounds shown below are prepared according to Example A9 by introduction of the 2-cyano substituent to a variety of readily available substituted 4-phenylpyridines with separation of isomers where necessary, followed by hydrolysis, reestrification with anhydrous acidic ethanol and hydrogenation of the pyridine ring to prepare the following intermediates:

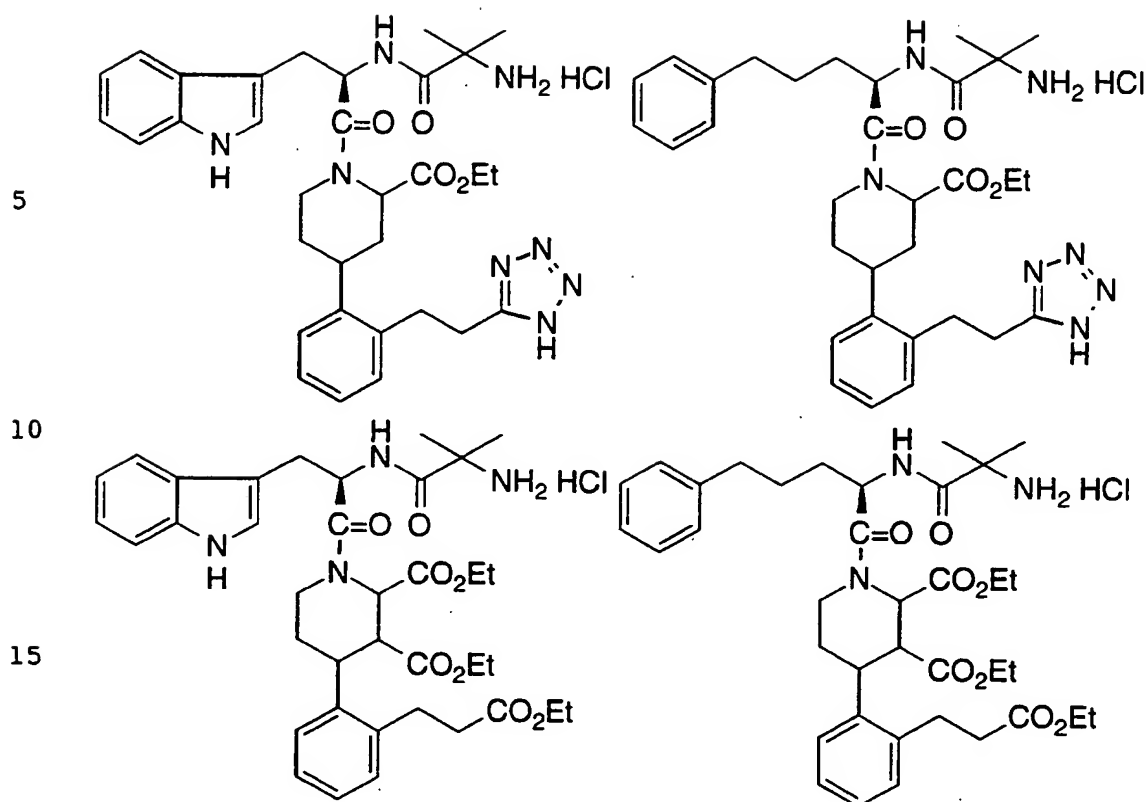
- 123 -



15 which may be reacted with Intermediate 1 or 3 to give the following compounds respectively.



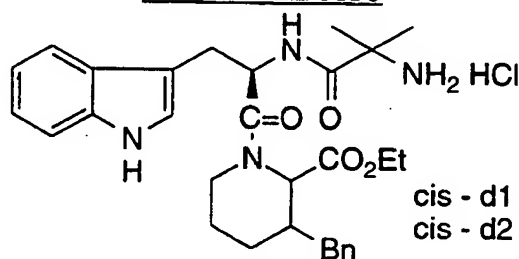
- 124 -



20

EXAMPLE A10

25

Step A: 3-Benzylpyridine N-oxide

30 A solution of 3-benzylpyridine (25 g, 0.148 mol) in hydrogen peroxide (30%, 15.1 mL) and acetic acid (100 mL) was refluxed for one day. Then more hydrogen peroxide (3 mL) was added and the resulting mixture was refluxed overnight. The reaction mixture was then evaporated and partitioned between a mixture of 3 N HCl, brine and dichloromethane. The organic layer was separated, dried and evaporated to give the desired compound (27.6 g, 100%).

- 125 -

Step B: 3-Benzyl-2-cyanopyridine

Prepared according to the procedure in Example A9 step A from the intermediate from the previous step (27 g). The crude reaction product was purified by a SiO₂ flash column eluting with 20-40% ethyl acetate in hexane to give 5-benzyl-2-cyanopyridine (3.0g, 10%) and 3-benzyl-2-cyanopyridine (24.2 g, 85%).

Step C: 3-Benzylpyridine-2-carboxylic acid hydrochloride

A solution of 3-benzyl-2-cyanopyridine (19.1 g) in concentrated hydrochloric acid (50 mL) and water (50 mL) was refluxed for two days. The resulting solution was evaporated to give a solid (30.1g 100%, which contains an equal molar amount of ammonium chloride).

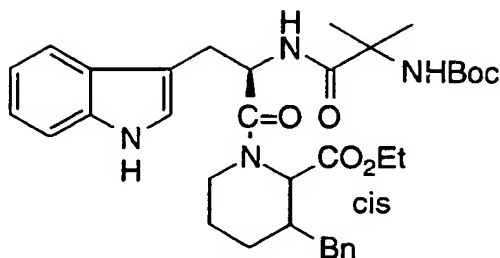
Step D: Ethyl 3-benzylpyridine-2-carboxylate hydrochloride

Thionyl chloride (15.2 g) was carefully dissolved in ethanol (300 mL) and the resulting solution was added to the intermediate from the previous step (20 g). The mixture was refluxed overnight and then evaporated to give the crude product as hydrochloride salt. The crude product was dissolved in dichloromethane and washed with saturated sodium bicarbonate. The organic solution was dried, evaporated and purified with a short SiO₂ column to give the product as free base (18.2 g). To a solution of this intermediate (16.5 g) in ethyl acetate (80 mL), was bubbled HCl gas until it was saturated. The mixture was then evaporated to give the HCl salt (18.9 g).

Step E: Ethyl 3-benzylpiperidine-2-carboxylate hydrochloride

A suspension of the product from the previous step (1.0 g) and platinum dioxide (100 mg) in ethanol was stirred under a hydrogen balloon for five hours. The reaction mixture was then filtered through celite and evaporated to give the desired compound.

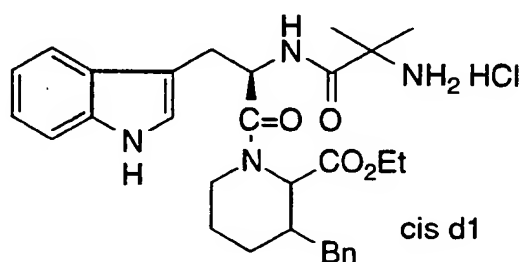
- 126 -

Step F:

To a solution of the intermediate prepared in the previous step (180 mg, 0.634 mmol), and Intermediate 1 (1 eq.), HOBT (1 eq.) and NMM (1 eq.) in dichloromethane, was added EDC (1.5 eq.) at 0°C. The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 50% ethyl acetate in hexane provided two enantiomerically pure compounds. The compound which came out first from the column was designated as d1 (146 mg); and the compound which came out of the column second was designated as d2 (141 g).

d1 FAB-MS calc. for C₃₅H₄₆N₄O₆: 618; Found 619 (M+H)

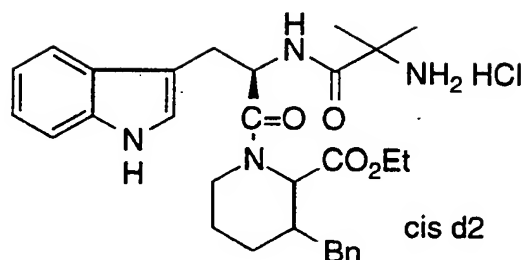
d2 FAB-MS calc. for C₃₅H₄₆N₄O₆: 618; Found 619 (M+H)

Step G:

To a stirred solution of the intermediate d1 from the previous step (130 mg) in ethyl acetate (2 mL) at 0°C, was bubbled HCl gas until it was saturated. The reaction mixture was stirred for 15 minutes and it was evaporated to dryness to give the product (111 mg, 95%)

FAB-MS calc. for C₃₀H₃₈N₄O₄: 518; Found 519 (M+H)

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Step H:

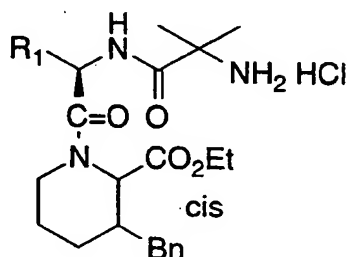
The compound was prepared according to the procedure of the previous step from the intermediate d2 from Step F (130 mg).

Product: 114 mg, 98%

FAB-MS calc. for $C_{30}H_{38}N_4O_4$: 518; Found 519 (M+H)

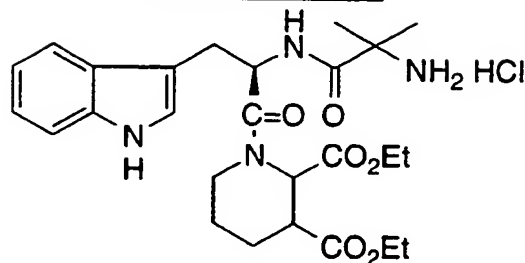
The additional products shown in Table AII were prepared according to Example A10 Steps F and G, using Intermediate 2 or Intermediate 3 and the intermediate from step E. No separation of the diastereoisomers was observed during MPLC purification of the Boc precursor.

TABLE AII: ADDITIONAL EXAMPLES

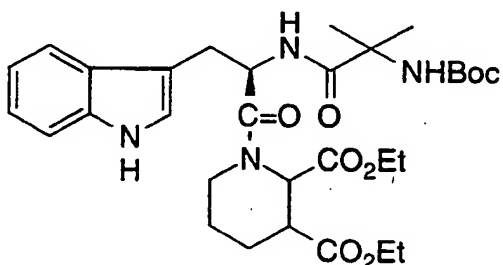


| | | Product |
|-------|--------------------------------------|--|
| entry | R1 | MF |
| | | FAB-MS (M+1) |
| 1 | Ph(CH ₂) ₃ - | C ₃₀ H ₄₁ N ₃ O ₄ 508 |
| 2 | PhCH ₂ OCH ₂ - | C ₂₉ H ₃₉ N ₃ O ₅ 510 |

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EXAMPLE A11Step A: Diethyl piperidine-2,3-(cis)-dicarboxylate

Hydrogen chloride gas was bubbled into ethanol (400 mL) until 22 g was absorbed. Pyridine-2,3-dicarboxylic acid (100 g) was dissolved in this solution and the resulting mixture was refluxed overnight. The reaction mixture was divided into two portions and each was shaken with PtO₂ (1.4 g) in Parr shakers under 40 psi of hydrogen for 8 hours. The reaction mixture was combined and filtered through celite and washed with plenty of ethanol. Evaporation gave a gray solid which was washed with ethyl acetate to give a white solid after filtration (74.8 g)

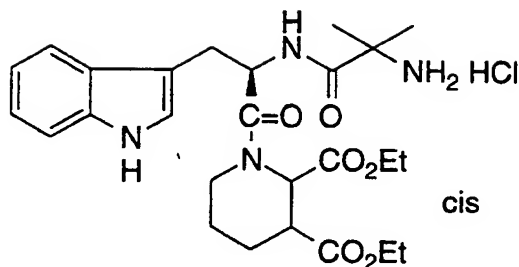
Step B:

The compound was prepared according to the procedure of Example A1 Step A from the intermediate from the previous step (178 mg) and Intermediate 1. Product: 234 mg FAB-MS calc. for C₃₁H₄₄N₄O₈: 600 ; Found 601(M+H)

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Step C:

5

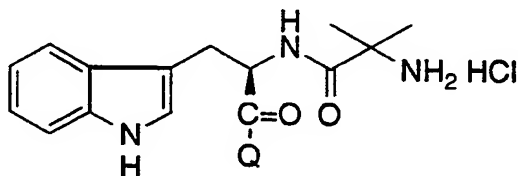


The compound was prepared according to the procedure of
 Example A1 Step B from the intermediate from the previous step (230
 10 mg). Product: 215 mg
 FAB-MS calc. for C₂₆H₃₆N₄O₆: 500 ; Found 501(M+H), 523 (M+Na)

The additional intermediates shown in Table AIII were
 prepared from the corresponding pyridine analogs according to the above
 15 established procedures from the corresponding pyridine derivatives as
 exemplified in Example A11 step A and the final products were prepared
 according to Steps B and C

TABLE AIII: ADDITIONAL EXAMPLES

20



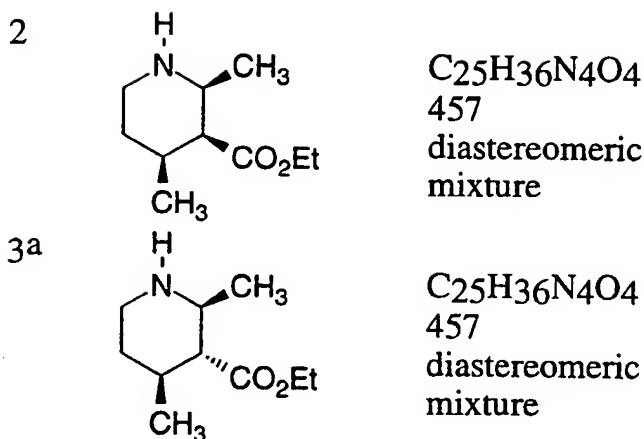
25

Product

30

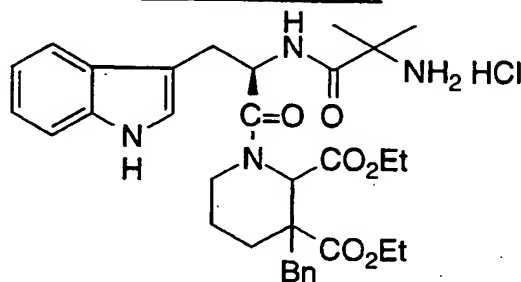
| Intermediate (QH) | | Product |
|-------------------|--------------|---|
| entry | MF | MF |
| | FAB-MS (M+1) | FAB-MS (M+1) |
| 1 | | C ₂₄ H ₃₄ N ₄ O ₄ 443 diastereomeric mixture |

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a: The intermediate was prepared by epimerization of its all cis isomer with KHMDS in THF.

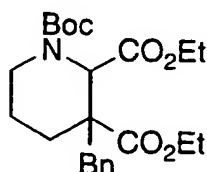
EXAMPLE A12



Step A: Diethyl N-Boc-piperidine-(cis)-2,3-dicarboxylate

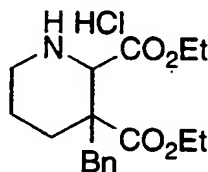
To a stirred solution of the intermediate from Example A11 Step A (10 g, 37.6 mmol) and triethylamine (6.4 mL) in dichloromethane (50 mL), was added di-*t*-butyl dicarbonate (10.7 g) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and was washed with a mixture of 3 N HCl and brine. The organic layer was dried, evaporated and purified with a silica gel column eluting with a gradient of 10-30% ethyl acetate in hexane to give the desired compound (9.61 g).

Step B:

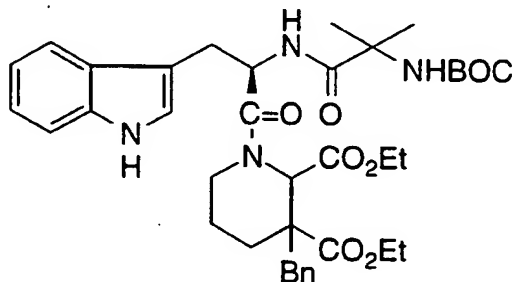


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To a stirred solution of KHMDS (3.79, 19 mmol) in THF (150 mL) at -78°C under argon was added a solution of diethyl N-Boc-piperidine-(cis)-2,3-dicarboxylate (5 g, 15.2 mmol) over a 30 minute period. The solution was allowed to stir an additional 30 minutes at -78°C; then benzyl bromide (2.73 g, 15.9 mmol) was added slowly to the solution. The reaction mixture was stirred overnight and allowed to warm to room temperature. The material was concentrated, then diluted with water, and extracted with ethyl acetate (100 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by silica gel flash column chromatography, eluting with 20% ethyl acetate in hexane provided two diastereoisomers. The compound which came out first from the column was designated as d1 (1.01 g); and the compound which came out of the column second was designated as d2 (3.75 g). NMR established the esters are trans in d1 and cis in d2.

Step C:

The compounds were prepared according to the procedure of Example A1 Step B from the intermediates from the previous step. Intermediate d1 (850 mg) yielded the d1 title compound (711 mg, 98%). Intermediate d2 (3.2 g) yielded the d2 title compound (2.58 g, 96%).
d1 FAB-MS calc. for C₁₈H₂₅NO₄: 319 ; Found 320(M+H)
d2 FAB-MS calc. for C₁₈H₂₅NO₄: 319 ; Found 320(M+H)

Step D:

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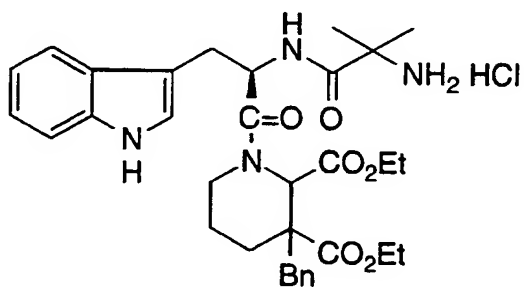
The compounds were prepared according to the procedure of Example A1 Step A from the intermediates from the previous step.

Intermediate d1 (228 mg) yielded a mixture of trans diastereomers (128 mg, 30%).

5 Intermediate d2 (228 mg) yielded a mixture of cis diastereomers (164 mg, 30%).

Step E:

10



15

The compounds were prepared according to the procedure of Example A1 Step B from the intermediates from the previous step.

Intermediate d1 (120 mg) yielded the title compound as mixture of trans (d1) diastereomers (106 mg, 97%).

20 Intermediate d2 (155 mg) yielded the title compound as mixture of cis (d2) diastereomers (135 mg, 96%).

d1 FAB-MS calc. for C₃₃H₄₂N₄O₆: 590 ; Found 591(M+H)

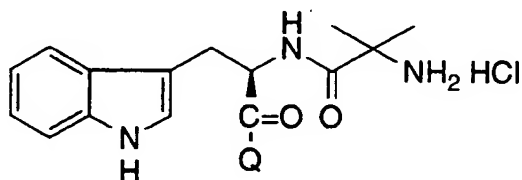
d2 FAB-MS calc. for C₃₃H₄₂N₄O₆: 590 ; Found 591(M+H)

25

The additional intermediates shown in Table AIV were prepared according to the above established procedures using N-Boc intermediates from Table AIII as exemplified in Example A12 Steps A, B and C and the final products were prepared according to Steps D and E.

30

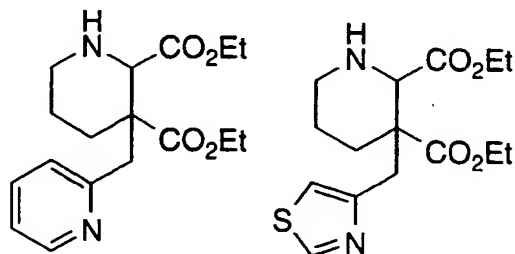
- 133 -

TABLE AIV: ADDITIONAL EXAMPLES

Product

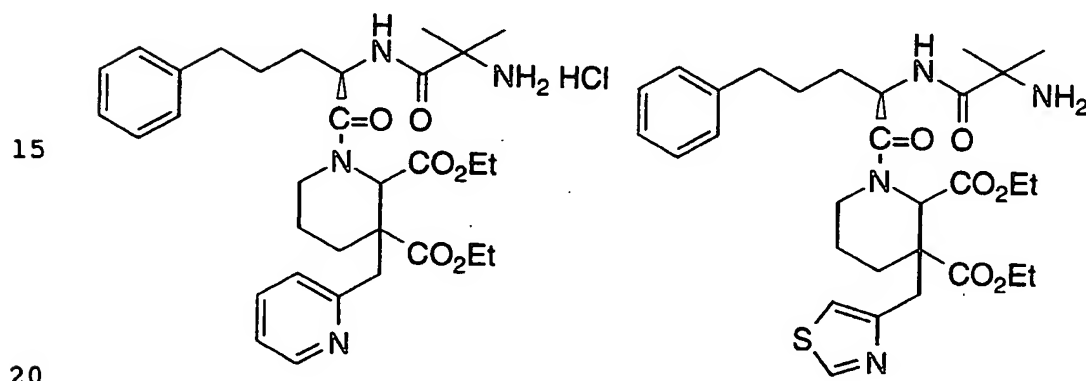
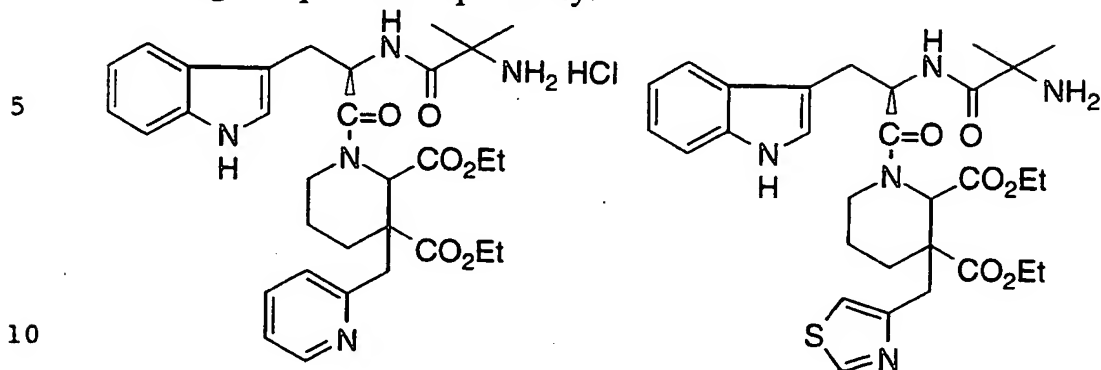
| entry | Intermediate (QH) | Product |
|-------|-------------------|---|
| | MF | MF |
| | FAB-MS (M+1) | FAB-MS (M+1) |
| 1 | | d1: C ₃₁ H ₄₀ N ₄ O ₄ 533 |
| 2 | | d2: C ₃₁ H ₄₀ N ₄ O ₄ 533 |
| 3 | | mixture of diastereomers C ₃₂ H ₄₂ N ₄ O ₄ 547 |

Likewise the compounds shown below are prepared according to Example A12 by alkylating with 2-picolyl chloride or 4-bromomethylthiazole to give the following intermediates:

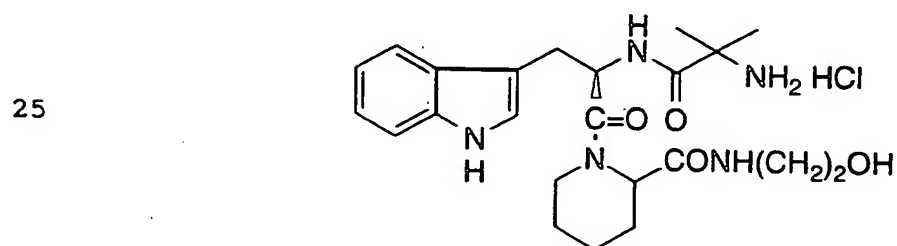


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which may then be reacted with Intermediates 1 or 2 to give the following compounds respectively:



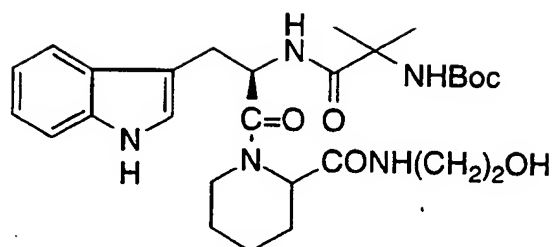
EXAMPLE A13



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Step A:

5



10 To a stirred solution of dl-2-pipecolamidoethanol (100 mg, (1.16 mmol), HOBT (78.38 mg, 1.16 mmol) and Intermediate 1 (226.12 mg, 1.16 mmol) in dichloromethane (3ml) at ambient temperature was added 4-methyl morpholine (63.8 ml, (1.16 mmol). The mixture was cooled to 0° C and to which was added EDC (222.3 mg, 2.32 mmol). The reaction mixture was stirred at room temperature for 16 h. After

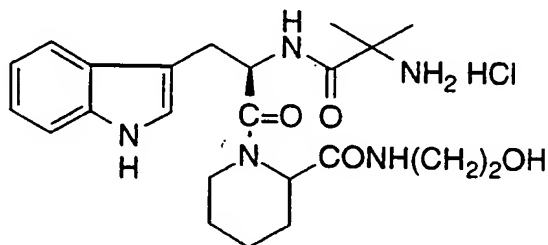
15 evaporation, the residue was partitioned in ethyl acetate and 1N hydrochloric acid. The organic layer was washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered, and evaporated to an oily foam which was purified by preparative tlc (acetone/chloroform: 3/7) to give 91 mg of the product ($R_f = 0.45$).

20 CI-MS : calc. for $C_{28}H_{41}N_5O_6$: 543 ; Found 544(M+H)
 1H NMR (400 MHz, $CDCl_3$): δ 8.35 (br.s, 1H), 7.57 & 7.55 (2s, 1H), 7.35, 7.33, (2s, 2H), 7.17 (t, $J = 6.95$ Hz, 1H), 7.15-7.07 (m, 3H), 7.03 (distorted t, $J = 4.95$ Hz, 1H), 5.16 (d, $J = 4.68$ Hz, 1H), 4.94 (m, 2H), 3.65 (m, 2H), 3.55-3.10 (m, 5H), 2.9-2.62 (m, 4H), 2.3-2.2 (m, 1H), 1.43, 1.46 and 1.41 (3 s, total 15H), 1.00 (m, 1H), 0.83 (m, 1H).

25

Step B:

30



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Prepared according to the experimental procedure from Example A1 Step B using product from the previous step and HCl gas in ethyl acetate at 0°C.

CI-MS : calc. for C₂₃H₃₃N₅O₄: 443 ; Found 444(M+H)

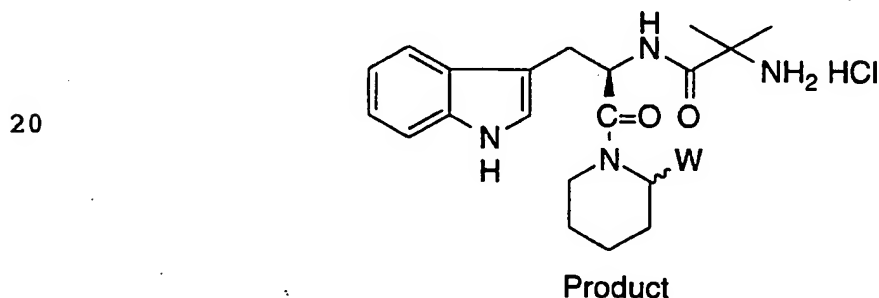
5 ¹H NMR (400 MHz, CD₃OD): δ 7.54 (d, J=7.7 Hz, 1H), 7.36 (d, J=8.1 Hz), 7.12 (distorted t, J=7.5 Hz, 1H), 7.03 (distorted t, J=7.5 Hz, 1H), 4.97-4.92 (m, 1H), 3.63 (m, 1H), 3.75 (br. d, 1H), 2.82 (br. t, J=2.3 Hz, 1H), 2.07 (br. d, J=2.3 Hz, 1H), 1.66-1.57 (m, 6H), 1.55-0.88 (m, 4H), 0.70-0.55 (m, 1H).

10

The additional compounds shown in Table AV were prepared according to Steps A and B using Intermediate 1. The piperidine intermediates were either commercially available or were prepared according to the above established procedures or from literature procedures.

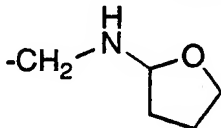
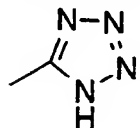
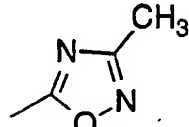
15

TABLE AV: ADDITIONAL EXAMPLES



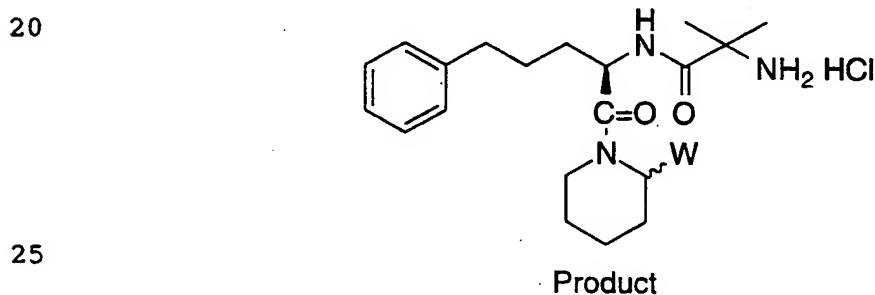
| 25 | W | MF | FAB(or CI)-MS (M+1) |
|------|--|--|---------------------------|
| 1 | -CO ₂ CH ₃ | C ₂₂ H ₃₀ N ₄ O ₄ | 415 |
| 2 | -CONH(CH ₂) ₂ OH | C ₂₃ H ₃₃ N ₅ O ₄ | 444 |
| 3 | -CONHCH ₂ C(CH ₃) ₂ OH | C ₂₅ H ₃₇ N ₅ O ₄ | 472 |
| 30 4 | -CONHCH ₂ CH(OH)CH ₃ | C ₂₄ H ₃₅ N ₅ O ₄ | 458 |
| 5 | -CO ₂ NH ₂ | C ₂₁ H ₂₉ N ₅ O ₃ | 399 (EI, M ⁺) |
| 6 | -CH ₂ COCH ₃ | C ₂₃ H ₃₂ N ₃ O ₄ | 413 |
| 7 | -CH(OH)Ph- <i>p</i> -Cl | C ₂₇ H ₃₃ N ₄ O ₃ Cl | 497 |
| 8 | -CH(OH)CH ₂ CH ₃ | C ₂₃ H ₃₄ N ₄ O ₃ | 415 |

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| | | | |
|----|---|---|-----|
| 9 | -CONHBn | C ₂₈ H ₃₅ N ₅ O ₃ | 490 |
| 10 | -CONH(CH ₂) ₂ CH ₃ | C ₂₄ H ₃₅ N ₅ O ₃ | 442 |
| 11 |  | C ₂₅ H ₃₇ N ₅ O ₃ | 456 |
| 12 | -CONHPh | C ₂₇ H ₃₃ N ₅ O ₃ | 476 |
| 13 |  | C ₂₁ H ₂₈ N ₈ O ₂ | 425 |
| 14 |  | C ₂₃ H ₃₀ N ₆ O ₃ | 439 |

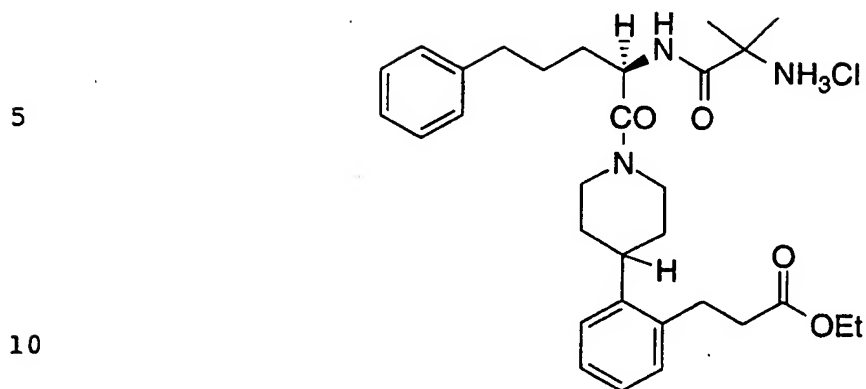
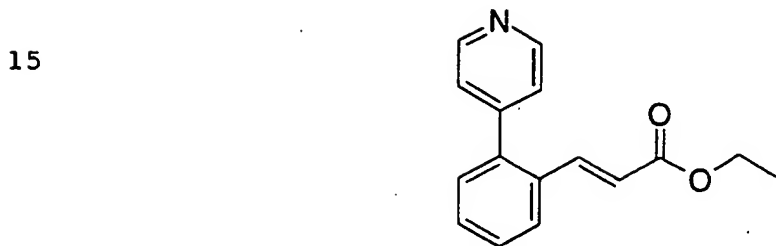
The additional compounds shown in Table AVa were prepared according to Steps A and B using Intermediate 3 and some of intermediates used in the previous table.

TABLE AVa: ADDITIONAL EXAMPLES



| | W | MF | FAB(or CI)-MS (M+1) |
|---|--|--|------------------------|
| 1 | -CO ₂ CH ₂ CH ₃ | C ₂₃ H ₃₅ N ₃ O ₄ | 418 |
| 2 | -CONHCH ₂ C(CH ₃) ₂ OH | C ₂₅ H ₄₀ N ₄ O ₄ | 461 |
| 3 | -CONH(CH ₃) ₂ | C ₂₃ H ₃₃ N ₅ O ₃ | 428 |
| 4 | -CH(OH)Ph- <i>p</i> -Cl | C ₂₇ H ₃₆ N ₃ O ₃ Cl | 486 |

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EXAMPLE B1Step A:

To 7.0 g of 2-bromobenzyl alcohol in 7.0 g of dihydropyran at room temperature was added 2 drops of concentrated hydrochloric acid and stirred at room temperature for 1h. The reaction mixture was diluted with 150 mL of ether and washed with saturated NaHCO₃ (2X100 mL),
25 brine (150 mL), dried over MgSO₄ and concentrated to give a thick oily material. The residue was purified by flash chromatography with hexane-EtOAc as eluent to give 10 g of the tetrahydropyranyl ether.

To 260 mL of dry ether at -78°C was added 23.6 mL of 1.6 M solution of nBuLi in hexanes. To this solution was added a solution of
30 7.5 g of the THP compound in 100 mL of ether and stirred at -78°C for 30 min. and -40°C for an additional 30 min. This solution was added in a dropwise manner to a mixture of 2.16 g of pyridine and 6.3 mL of t-butyldimethyl-silyl triflate in 200 mL of ether at -78°C. The reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction was quenched with 75 mL of water and oxygen

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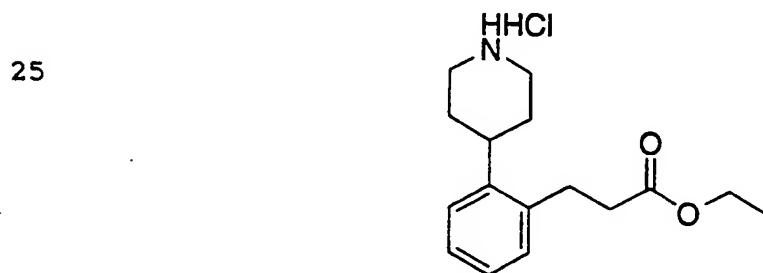
gas was bubbled in for 3h. The reaction mixture was diluted with ether and 3N HCl till the pH = 1 and then the organic layer was separated. The aqueous layer was basified with 20% NaOH till the pH = 8-9 and then extracted with chloroform (3X100 mL). The organic layer was washed
5 with water, brine (200 mL), dried over Na₂SO₄, filtered, and evaporated.

To 3.42 g of the above compound in 100 mL of CHCl₃ was added 30 g of activated manganese dioxide and stirred overnight. The solids were filtered off through a pad of celite, and the filtrate was evaporated.

10 To 2.4 mL of triethylphosphonoacetate in 30 mL of dry THF at 0°C was added 16.3 mL of a solution of sodium hexamethyldisilazide in THF and stirred for 30 min. A solution of the above aldehyde intermediate in 10 mL of THF was added and stirred for 30 min. The reaction was quenched with 25 mL of saturated NH₄Cl solution, and
15 extracted with EtOAc(3X25 mL). The combined organics were washed with brine, dried over Na₂SO₄, and concentrated. Flash chromatography of the residue with hexane-EtOAc (4:1) as eluent gave 1.5 g of the desired product as a pale yellow solid.

20 ¹H NMR (CDCl₃, 400MHz) δ 8.63 (d, 2H), 7.68 (dd, 1H), 7.60 (d, 1H), 7.45-7.35 (m, 2H), 7.30 (dd, 1H), 7.35 (d, 1H), 4.15 (q, 2H), 1.23 (t, 3H).

Step B:



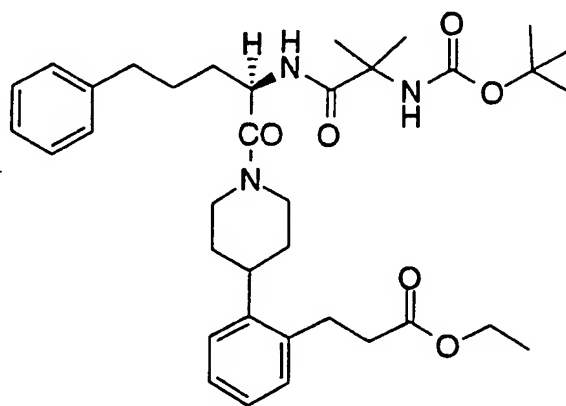
To 1.5 g of the above intermediate in 25 mL of methanol was added 5 mL of 4M HCl in EtOAc and evaporated to dryness. This solid was dissolved in 30 mL of methanol and 0.50 g of PtO₂ was added and hydrogenated at 50 psi for 5h. The catalyst was filtered off through a pad of celite and the filtrate was concentrated to give the title compound.

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¹H NMR indicated that this material contained about 5% of the cyclohexyl-piperidine.

¹H NMR (CD₃OD, 400MHz) δ 7.40-7.20 (m, 4H), 4.08 (q, 2H), 3.50 (m, 2H), 3.25-3.10 (m, 3H), 3.00 (t, 2H), 2.60 (t, 2H), 2.03-1.90 (m, 4H), 1.20 (t, 3H).

Step C:



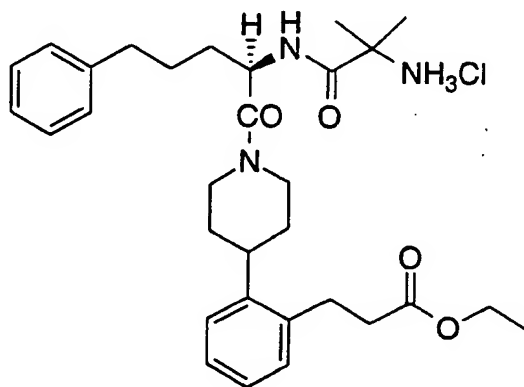
To a mixture of the above intermediate in 30 mL of CH₂Cl₂ was added 0.82 mL of triethylamine, 1.2 mL of NMM, 0.90 g of HOBT, 2.13 g of (2R)-N-tBOC-5-phenylpentanoic acid (prepared as described in H. K. Chenault et al. *J. Am. Chem. Soc.*, 111, 6354-6364 (1989)), and finally 1.7 g of EDC and stirred at room temperature for 18h. The reaction mixture was poured into a saturated NaHCO₃ solution and extracted with CH₂Cl₂. The combined organics were washed with 0.1N HCl, brine, dried over Na₂SO₄, and concentrated.

The above crude material was dissolved in 30 mL of CH₂Cl₂ and 10 mL of TFA was added and stirred at RT for 1h. The solvent was evaporated to dryness and the residue was neutralized with aqueous Na₂CO₃ solution, and extracted with CH₂Cl₂. The combined organics were washed with brine, dried over K₂CO₃, and concentrated. To a mixture of this intermediate in 30 mL of CH₂Cl₂ was added 1.04 g of HOBT, 1.56 g of N-tBOC-α-methylalanine, and finally 1.8 g of EDC and stirred at room temperature for 4h. The reaction mixture was poured in saturated NaHCO₃ solution and extracted with CH₂Cl₂. The

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combined organics were washed with 0.1N HCl, brine, dried over MgSO₄, and concentrated. Flash chromatography of the oily residue with CH₂Cl₂-acetone-ether (6:1:1) as eluent gave the desired material. ¹H NMR (CDCl₃, 400MHz) δ 7.30-6.98 (m, 9H), 5.00-4.85 (m, 2H), 4.72-4.64 (m, 1H), 4.13 (2q, 2H), 4.00-3.82 (m, 1H), 3.14-2.85 (m, 4H), 2.7-2.50 (m, 5H), 1.83-1.50 (m, 5H), 1.50 (s, 3H), 1.46 (s, 1.5H), 1.44 (s, 1.5H), 1.40 (s, 9H), 1.40-1.28 (m, 1H), 1.23 (2t, 3H).

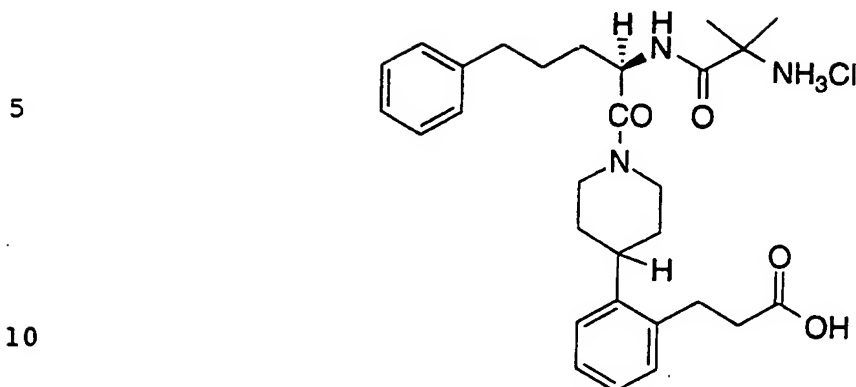
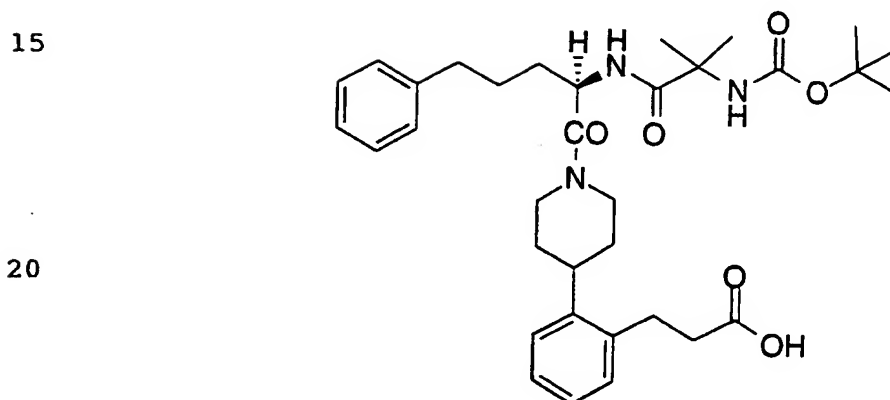
Step D:



To 1.70 g of the intermediate in Step C in 30 mL of CH₂Cl₂ was added 10 mL of TFA and stirred at RT for 1h. The reaction was evaporated to dryness, basified with aqueous Na₂CO₃, and extracted with CH₂Cl₂. The combined organics were washed with brine, dried over K₂CO₃, filtered, and evaporated to give free base as a thick oil. This material was dissolved in 5 mL of ether at 0°C and 0.50 mL of 4M HCl in EtOAc was added. The precipitate was filtered under an N₂ atmosphere and dried to give the title compound.

¹H NMR (CD₃OD, 400MHz) δ 7.30-6.98 (m, 9H), 5.00-4.85 (m, 2H), 4.72-4.64 (m, 1H), 4.13 (2q, 2H), 4.00-3.82 (m, 1H), 3.14-2.85 (m, 4H), 2.7-2.50 (m, 5H), 1.83-1.50 (m, 5H), 1.50 (s, 3H), 1.46 (s, 1.5H), 1.44 (s, 1.5H), 1.40-1.28 (m, 1H), 1.23 (2t, 3H).

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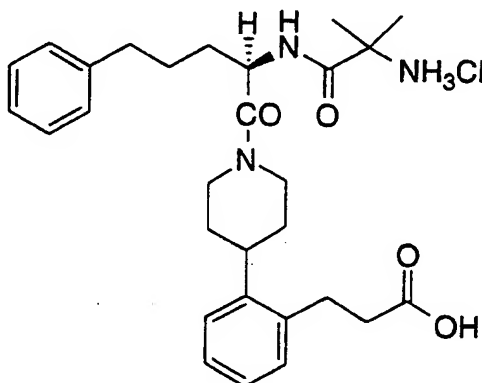
EXAMPLE B2Step A:

25 To a solution of 0.20 g of the intermediate from Example B1, Step C in 5 mL of anhydrous THF was added 46 mg of potassium trimethylsilanoate. After 2h an additional 46 mg of potassium trimethylsilanoate and 2 mL of THF were added and stirred at RT overnight. The reaction was diluted with 10 ml of water and washed with ether (2X10 mL). The aqueous layer was acidified with 0.1N HCl to
30 pH=2 and extracted with CH₂Cl₂ (2X15 mL). The combined organics were washed with brine, dried over Na₂SO₄, filtered and concentrated. Flash chromatography of the residue with CHCl₃-MeOH-NH₄OH (85:15:1) as the eluent gave 56 mg of the desired material.

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¹H NMR (CDCl₃, 400MHz) d 7.32-7.20 (m, 4H), 7.20-6.98 (m, 5H), 5.10 (bs, 1H), 5.00-4.90 (m, 1H), 4.65 (bt, 1H), 4.90 (dd, 1H), 3.10-2.85 (m, 4H), 2.70-2.50 (m, 5H), 1.80-1.50 (m, 5H), 1.50 (s, 4H), 1.46 (s, 1H), 1.42 (s, 1H), 1.38 (s, 9H), 1.35-1.20 (m, 1H).

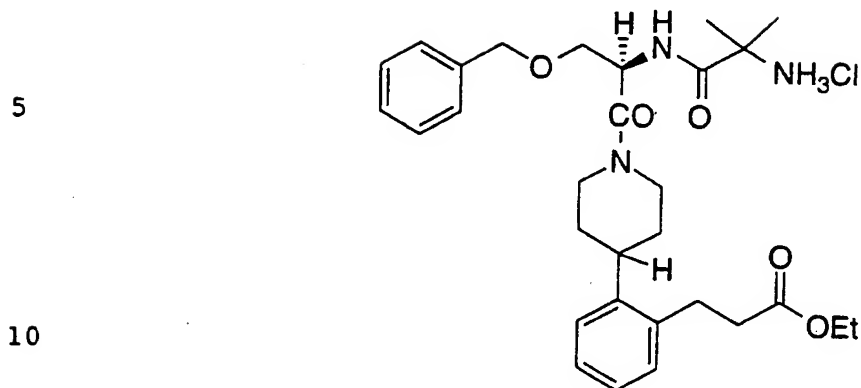
Step B:



To the above intermediate at RT was added 2 mL of 4M HCl in EtOAc maintained at RT for 2h. The reaction was evaporated to dryness and the residue was triturated with ether to give the title compound as a white solid.

¹H NMR (CD₃OD, 400MHz) d 8.15 (t, 1H), 7.30-7.00 (m, 9H), 4.90 (m, 1H), 4.60 (bd, 1H), 4.05 (d, 1/2H), 3.95 (d, 1/2H), 3.25-3.05 (m, 2H), 3.00 (dt, 2H), 2.80-2.50 (m, 5H), 1.85-1.63 (m, 6H), 1.63 (s, 2H), 1.60 (s, 4H), 1.60-1.20 (m, 2H).

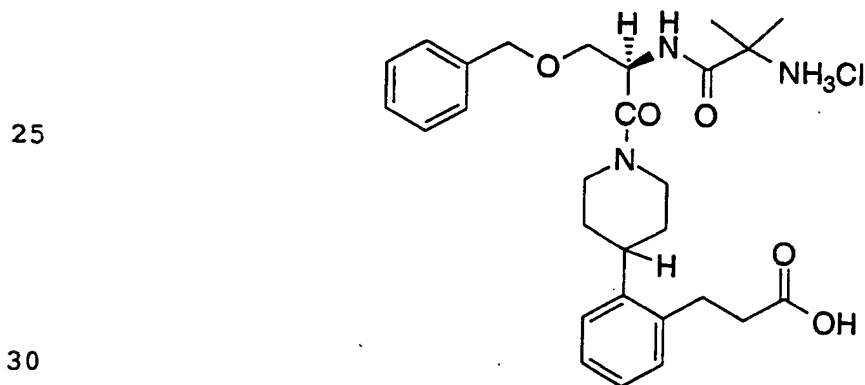
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EXAMPLE B3

The title compound was prepared as described in Example B1 Steps C and D, but commercially available N-t-BOC-O-benzyl-D-serine was substituted for (R)-2-N-t-BOC-5-phenylpentanoic acid.

15 ¹H NMR (CD₃OD, 400MHz) δ 8.30 (d, 1/2H), 8.23 (d, 1/2H), 7.40-7.25 (m, 5H), 7.20-7.05 (m, 3.5H), 6.88 (d, 1/2H), 5.20 (m, 1H), 4.70-4.50 (m, 3H), 4.20-4.05 (m, 3H), 3.84-3.65 (m, 2H), 3.28-2.95 (m, 4H), 2.75 (q, 1H), 2.58 (dt, 2H), 1.85-1.70 (m, 2H), 1.64 (s, 2H), 1.61 (s, 4H), 1.55-1.40 (m, 2H), 1.20 (2t, 3H).

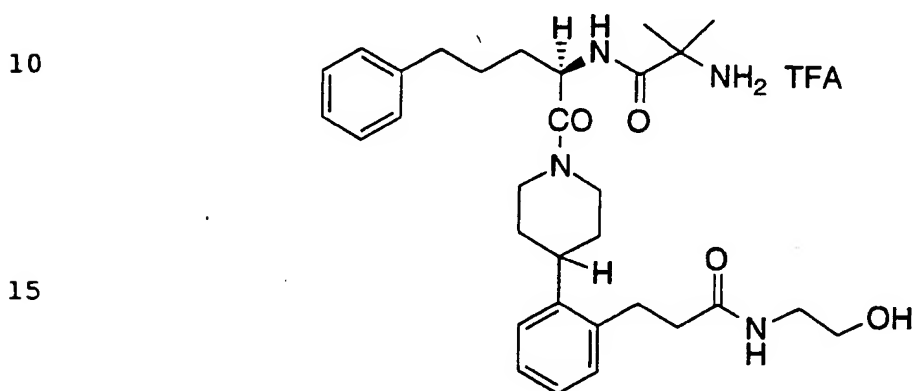
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EXAMPLE B4

To 54 mg of the compound prepared in Example B3 was added 2 mL of 2N aqueous HCl and stirred at RT overnight. The solvents were removed under reduced pressure and the residue was dried under vacuum to give the title compound.

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¹H NMR (CD₃OD, 400MHz) δ 8.30 (d, 1/2H), 8.23 (d, 1/2H), 7.40-7.25 (m, 5H), 7.20-7.05 (m, 3.5H), 6.88 (d, 1/2H), 5.20 (m, 1H), 4.70-4.50 (m, 3H), 4.20-4.05 (m, 1H), 3.84-3.65 (m, 2H), 3.28-2.95 (m, 4H), 2.75 (q, 1H), 2.58 (dt, 2H), 1.85-1.70 (m, 2H), 1.64 (s, 2H), 1.61 (s, 4H), 1.55-1.40 (m, 2H).

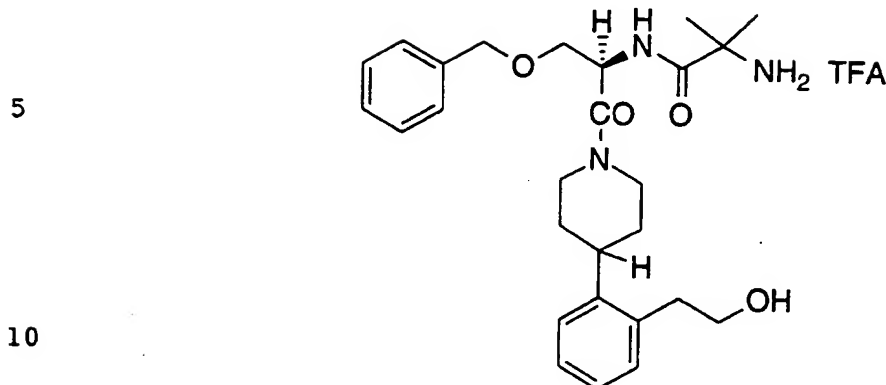
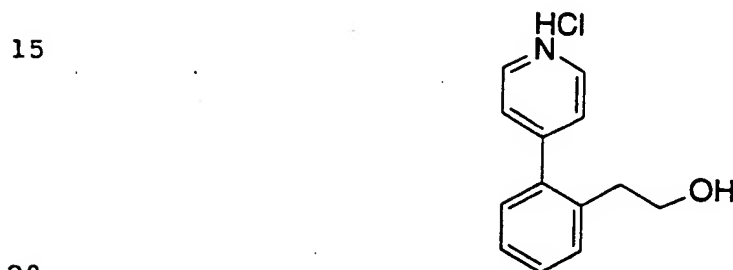
EXAMPLE B5

To a solution of 0.109 g of the intermediate obtained in Step A Example B2 in 3 mL of CH₂Cl₂ was added 0.017 mL of ethanolamine, 34 mg of HOBT, and 58 mg of EDC and stirred at RT overnight. The reaction mixture was diluted with 10 mL of CH₂Cl₂ and washed with 5 mL of 0.10N HCl, 5 mL of saturated aqueous NaHCO₃, dried over MgSO₄, and concentrated. Flash chromatography of the residue with CH₂Cl₂-acetone (3:2) as the eluent gave the coupled product.

As before, the above material was treated with CH₂Cl₂-TFA at RT for 30 min., evaporated to dryness, and triturated with ether to give the title compound as a pale yellow solid.

¹H NMR (CD₃OD, 400MHz) δ 8.15 (t, 1H), 7.30-7.00 (m, 9H), 4.95 (m, 1H), 4.60 (bd, 1H), 4.40 (bs, 1H), 4.00 (bdd, 1H), 3.60-3.50 (m, 2H), 3.40-3.10 (m, 4H), 3.05-2.90 (m, 2H), 2.85-2.60 (m, 5H), 2.52-2.40 (m, 4H), 1.90-1.65 (m, 6H), 1.63 (s, 2H), 1.60 (s, 4H), 1.60-1.20 (m, 2H).

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EXAMPLE B6Step A:

To 9.0 g of 2-bromophenethyl alcohol in 6.12 mL of dihydropyran at room temperature was added 2 drops of concentrated hydrochloric acid and stirred at room temperature for 1h. The reaction mixture was diluted with 150 mL of ether and washed with saturated NaHCO₃ (2X100 mL), brine (150 mL), dried over MgSO₄ and concentrated to give a thick oily material. The residue was purified by flash chromatography with hexane-EtOAc as eluent to give 10 g of the ether.

To 200 mL of dry ether at -78°C was added 17.7 mL of 1.6 M solution of nBuLi in hexanes. To this solution was added a solution of 8.0 g of the ether intermediate in 100 mL of tetrahydropyranyl ether and stirred at -78°C for 30 min. and -40°C for an additional 30 min. This solution was added in dropwise manner to a mixture of 2.16 g of pyridine and 6.3 mL of t-butyldimethylsilyl triflate in 200 mL of ether at -78°C.

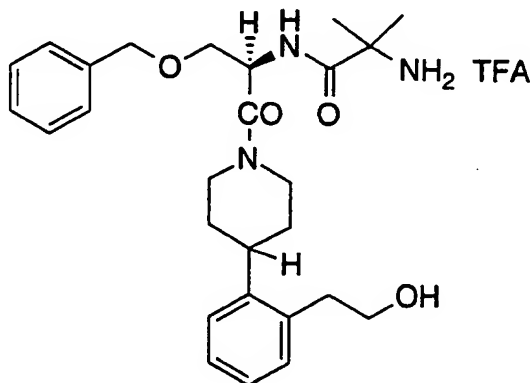
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The reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction was quenched with 75 mL of water and oxygen gas was bubbled in for 3h. The reaction mixture was diluted with ether and 3N HCl till the pH = 1 and then the organic layer was separated. The aqueous layer was basified with 20% NaOH till the pH = 8-9 and then extracted with chloroform (3X100 mL). The organic layer was washed with water, brine (200 mL), dried over Na₂SO₄, filtered, and evaporated. Flash chromatography of the residue with hexane-ethylacetate (1:1) as the eluent gave the desired product.

Approximately 0.90 g of the phenyl-pyridine intermediate prepared as described above was converted to the hydrochloride salt by treating it with 4M HCl in EtOAc.

¹H NMR (CDCl₃, 400MHz) δ 8.90 (d, 2H), 8.20 (dd, 1H), 7.73-7.35 (m, 4H), 3.70 (t, 2H), 2.83 (t, 2H).

Step B:



To 0.90 g of the above intermediate in 25 mL of methanol was added 0.10 g of PtO₂ and hydrogenated with pressurized hydrogen at 50 psi for 5h. The catalyst was filtered off and the filtrate was concentrated. The residue was treated with 1.4 g of di-*t*-butylcarbonate in 3 mL of dioxane, 1 mL of water, and 1 mL of triethylamine for 18h. The protected piperidine was separated by flash chromatography with CH₂Cl₂-acetone (10:1) as the eluent.

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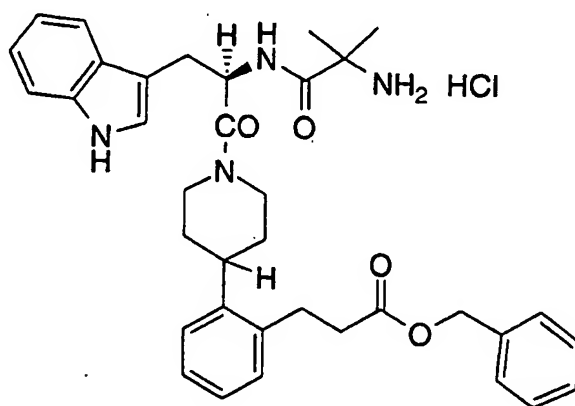
To 0.25 g of protected piperidine intermediate synthesized above was added 2 mL of CH₂Cl₂ and 0.50 mL of TFA and stirred at RT for 30 min. The reaction was evaporated to dryness and azeotroped with toluene.

To a solution of the above residue in 2 mL of CH₂Cl₂ was added 0.079 g of HOBt, 0.14 g of Intermediate 2, 0.070 mL of NMM, and 0.090 g of EDC and stirred at RT overnight. The reaction mixture was poured into saturated NaHCO₃ and extracted with CH₂Cl₂. The combined organics were washed with 0.5N HCl, brine, dried over MgSO₄, and concentrated. Flash chromatography of the residue with CH₂Cl₂-acetone (9:1) as the eluent gave the coupled product.

Deprotection of the N-t-butoxycarbonyl group was carried out by treating the above intermediate with 1 mL of TFA in 2 mL of CH₂Cl₂ for 2h. Concentration of the reaction mixture, trituration with ether and drying under vacuum gave the title compound as a colorless solid.

¹H NMR (CD₃OD, 400MHz) δ 7.40-6.88 (m, 9H), 5.17 (bs, 1H), 4.77-4.50 (m, 3H), 4.18 (bd, 1H), 3.80-3.65 (m, 4H), 3.30-3.05 (m, 4H), 2.95-2.70 (m, 2H), 1.85-1.60 (m, 2H), 1.60 (s, 2H), 1.58 (s, 4H), 1.70-1.45 (m, 2H).

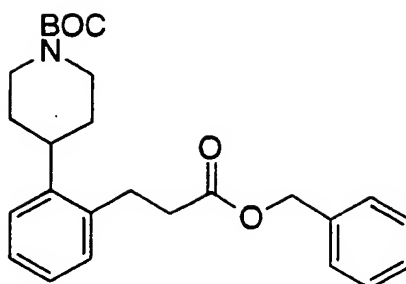
EXAMPLE B7



Step A:

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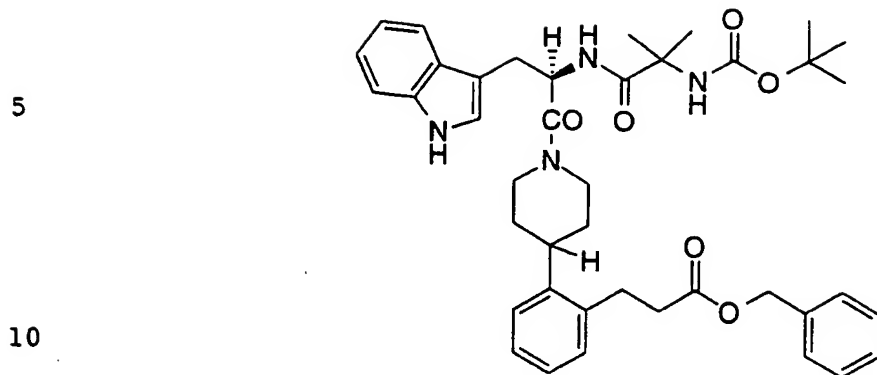


The PtO₂ reduction of the phenyl-piperidine intermediate prepared in Step A, Example B1 was attempted in different solvents like ethanol and methanol in the presence and absence of conc. HCl. Transesterification as well as unselective reduction of the pyridine was observed. Several of these reactions were combined and treated with excess di-*t*-butylcarbonate in CH₂Cl₂ and triethylamine. Approximately 5.0 g of the crude material thereby obtained after acid work-up was treated with 1.6 g of NaOH in 100 mL of methanol and 10 mL of water for 2h. The reaction mixture was diluted with water and washed with ether. The aqueous layer was acidified with 0.50N HCl till acidic and extracted with CHCl₃. The combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated. To about 4.0 g of this piperidine acid in 150 mL of CH₂Cl₂ at RT was added 1.86 mL of benzyl alcohol, 1.90 g of HOBT, 3.45 g of EDC and a catalytic amount of DMAP, and stirred at RT overnight. The reaction mixture was washed with saturated NaHCO₃, 0.50N HCl, brine, dried over Na₂SO₄, filtered and concentrated. The desired material was obtained after purification via flash chromatography.

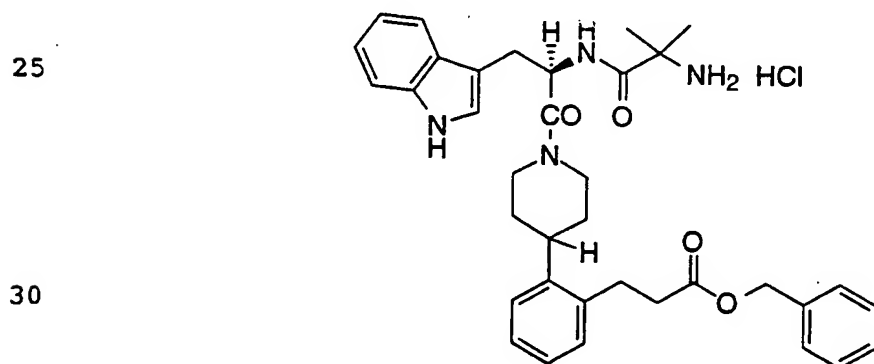
¹H NMR (CDCl₃, 400MHz) δ 7.40-7.28 (m, 5H), 7.22-7.10 (m, 4H), 5.12 (s, 2H), 4.25 (bs, 2H), 3.04 (t, 2H), 2.94-2.70 (m, 3H), 2.67 (t, 2H), 1.75-1.60 (m, 3H), 1.53 (s, 9H), 1.33-1.20 (m, 1H).

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Step B:

To a solution of 0.70 g of the above intermediate in 2.5 mL of CH_2Cl_2 was added 1 mL of TFA and the reaction mixture was stirred at RT for 1h. The reaction mixture was evaporated to dryness, dissolved in saturated aqueous NaHCO_3 , and extracted with CH_2Cl_2 . The combined organics were washed with brine, dried over K_2CO_3 , and concentrated. The residue was reacted with Intermediate 1 as described in Step B, Example B6. Flash chromatography of the residue with hexane-acetone-ether (6:1:1) as the eluent gave 0.47 g of the desired material.

Step C:

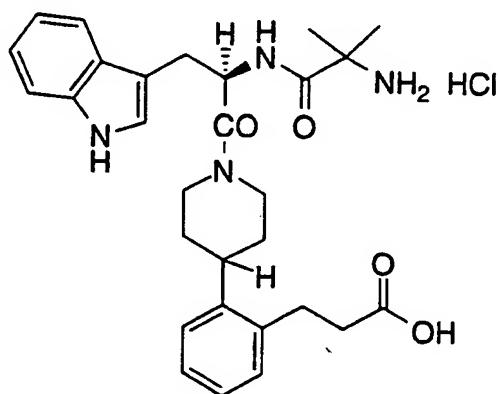
To a solution of 0.20 g of the above intermediate in EtOAc at 0°C was bubbled in HCl gas for about 10 seconds. The reaction mixture was capped and stirred for 30 min. Ether was added and the

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precipitate was filtered under an N₂ atmosphere. This gave 0.195 g of the title compound as a white solid.

The NMR indicated a 2:1 mixture of rotamers. ¹H NMR (CD₃OD, 400MHz) d 8.30 and 8.20 (2d, 1H), 7.53 and 7.45 (2d, 1H), 7.40 and 7.35 (2d, 1H), 7.30-7.00 (m, 11 and 1/3), 6.54 (d, 2/3H), 5.30-5.18 (m, 1H), 5.09 and 5.05 (2s, 2H), 4.60 and 4.55 (2d, 1H), 3.90 (2d, 1H), 3.35 (dd, 1H), 3.20 (dd, 1H), 3.00-2.85 (m, 3H), 2.75-2.40 (4H), 1.64 (s, 6H), 1.40 (d, 2/3H), 1.06 (d, 2/3H), 0.73 (dt, 1/3H), -0.03 (dt, 1/3H).

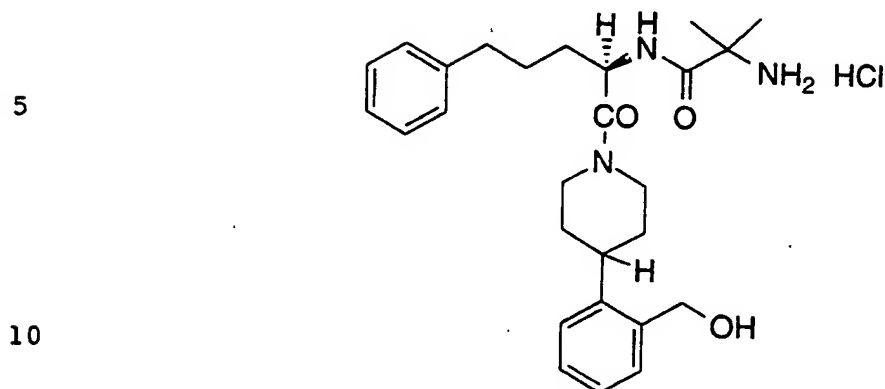
EXAMPLE B8



To a solution of 0.19 g of the intermediate from Step C, Example B7 in 3 mL of dioxane was added 50 mg of 10% Pd/C and hydrogenated under H₂ balloon for 3h. The reaction was slow so about 50 mg of 20% Pd(OH)₂/C was added and hydrogenated overnight. The catalyst was filtered off through a pad of celite and washed with dioxane. Evaporation of the filtrate gave the title compound as a pink solid.

The NMR indicated a 2:1 mixture of rotamers. ¹H NMR (CD₃OD, 400MHz) d 8.30 and 8.20 (2d, 1H), 7.53 and 7.45 (2d, 1H), 7.40 and 7.35 (2d, 1H), 7.20-7.00 (m, 6 and 1/3), 6.54 (d, 2/3H), 5.30-5.18 (m, 1H), 4.60 and 4.55 (2d, 1H), 3.90 (2d, 1H), 3.35 (dd, 1H), 3.20 (dd, 1H), 3.00-2.85 (m, 3H), 2.75-2.40 (4H), 1.64 (s, 6H), 1.40 (d, 2/3H), 1.06 (d, 2/3H), 0.73 (dt, 1/3H), -0.03 (dt, 1/3H).

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EXAMPLE B9

To 0.20 g of the benzyl alcohol-pyridine intermediate synthesized in Step A of Example B1 was added 2 mL of dry acetone and 0.10 mL of benzyl bromide and stirred at room temperature for 1 h. The volatiles were removed on the rotary evaporator and the residue was azeotroped with toluene. The residue was dissolved in methanol and treated with 0.10 g of sodium borohydride for 1 h. The reaction mixture was diluted with water and extracted with CH₂Cl₂. The combined organics were washed with brine, dried over magnesium sulfate, filtered, and evaporated. This gave a mixture of N-benzyl-tetrahydropyridines, which was hydrogenated in ethanol for 5 h with 10% Pd/C as the catalyst. The catalyst was filtered off and the filtrate was concentrated. Purification of the residue with CH₂Cl₂-methanol (90:10) as the eluent gave 70 mg of a mixture of tetrahydro- and hexahydropyridines. To a solution of 70 mg of the above mixture in 5 mL of CH₂Cl₂ was added 0.10 g of Intermediate 3, 0.040 g of HOBT and 0.070 g of EDC and stirred at RT overnight. The reaction mixture was poured into saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined organics were washed with brine, dried over Na₂SO₄, and concentrated. Purification of the residue by flash chromatography with hexane-EtOAc (4:1) as the eluent gave 0.090 g of the coupled product as a mixture of diastereomers.

The above coupled product was hydrogenated in ethanol with 10% Pd/C as the catalyst for 18 h. The catalyst was filtered off

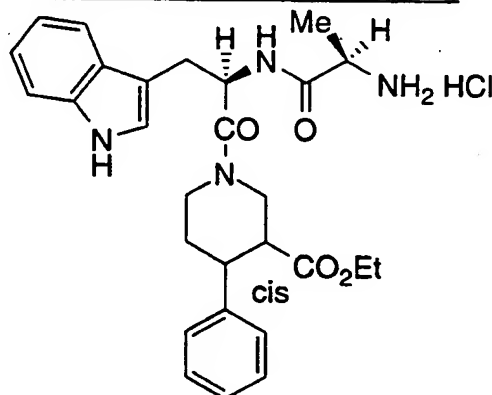
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through a pad of celite and the filtrate was concentrated. Flash chromatography of the residue with CH₂Cl₂-ether (6:1) as the eluent gave 90 mg of the desired product.

5 A final deprotection of the above intermediate was carried out in methanol (2 mL) in the presence of 1 mL of concentrated HCl for 5h. The reaction mixture was evaporated to dryness and the residue was triturated with ether to give a solid. Purification of this material by MPLC on an LH20 column with methanol as the eluent gave 34 mg of the title compound as a white solid.

10 ¹H NMR (CD₃OD, 400MHz) δ 7.35-7.04 (m, 9H), 4.95 (m, 1H), 4.69 (d, 2H), 4.60 (d, 1H), 3.97 (dd, 1H), 3.30-3.10 (m, 3H), 2.82-2.60 (m, 4H), 1.90-1.70 (m, 5H), 1.63 (s, 2H), 1.60 (s, 4H), 1.55-1.40 (m, 1H).

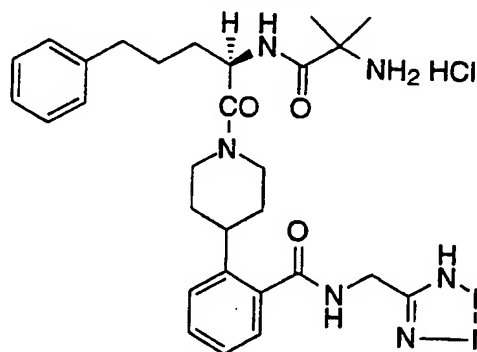
15 EXAMPLE B10 (cis, d1+d2)



30 The intermediate prepared from Example B12, Step B (930 mg, mixture of two diastereomers) was dissolved in methanol and hydrogenated over Pd(OH)₂ at one atmosphere for 12 hours. The mixture was filtered through Celite and the filtrate concentrated under vacuum to give 700 mg of deprotected product. To the residue (5.5 mg) in 0.5 ml of methylene chloride was added N-BOC-(D)-alanine (4.9 mg), EDC (5.0 mg) and HOBt (3.5 mg). After stirring overnight, the mixture was poured into water, extracted with methylene chloride and washed with brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by PLC (hexanes/ethyl acetate=1/1) to give coupling product. A final deprotection of the

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coupled intermediate was carried out by following the procedure described in Example B19, Step B to give 7.8 mg of desired compound. ¹H NMR (400 MHz, CD₃OD, mixture of diastereomers and rotamers): 7.59 (m, 1 H), 7.39-7.01 (m, 9 H), 5.37 (m, 1/2 H), 5.18 (m, 1/2 H), 4.61 (m, 1 H), 4.30 (m, 1/2 H), 4.02-3.61 (m, 3 H), 3.35-2.35 (m, 7 1/2 H), 1.60 (m, 1 H), 1.56 (d, 7 Hz 3/2H), 1.50 (m, 3/2H), 0.95 (m, 3/2 H), 0.88 (m, 3/2 H). FAB-MS: 491.0 (M+1).

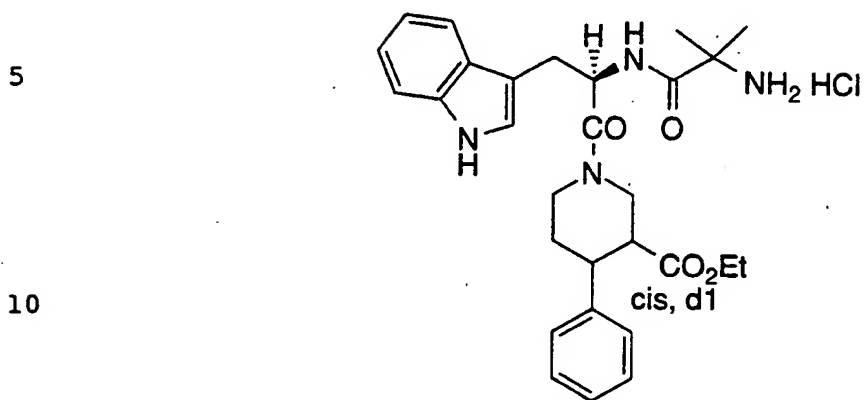
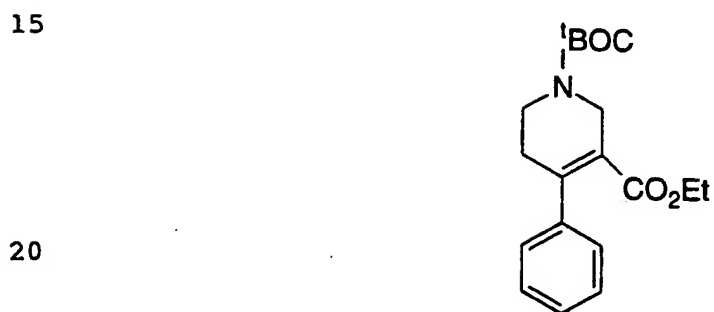
EXAMPLE B11

To a solution of 0.10g of the compound prepared in Step A of Example B15 in 2mL of chloroform at 0°C was added 0.018g of 5-aminomethyltetrazole, 0.027g of HOBT, 0.65mL of triethylamine and 0.048g of EDC and stirred for 10 min. at 0°C. 1mL of DMF was added to the suspension and stirred overnight. The reaction mixture was concentrated and the residue was separated by prep TLC (1mm plate) with CHCl₃-MeOH-NH₄OH (90:10:1) as the eluent to give the desired material. FAB MS m/e calcd. for C₃₄H₄₆N₈O₅ 646.36; found 647.2 (m+1).

To a cooled solution of 0.025g of the above product in 1mL of ethyl acetate was bubbled in HCl(gas) till it was saturated and allowed to stand at rt for 30 min. The reaction was concentrated to give the title compound.

¹H NMR (200MHz; CD₃OD) indicated a mixture of rotamers; 7.91 (d, J=8 Hz); 7.35-7.06 (m); 5.14 (bs); 4.65-4.48 (m); 3.92 (bt, J=13); 3.72-3.04 (m); 2.76-2.58 (m); 1.95-1.68 (m); 1.61 (s); 1.28 (s). FAB MS Calc. for C₃₄H₄₆N₈O₅ : MW=546.31; found m/e = (m+1) 547.1.

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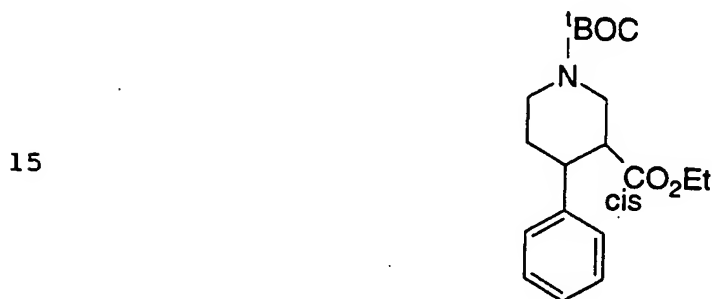
EXAMPLE B12 (cis, d1)Step A-1:

To a solution of 3-ethoxycarbonyl-4-piperidone hydrochloride (11.4 g, 54.9 mmole) in 82 ml of 1N aqueous sodium hydroxide was added di-t-butyl-dicarbonate (12.2 g, 56.0 mmole) in 82 ml of dioxane at room temperature. After 12 hours, the mixture was diluted with ethyl acetate and washed with 0.5 N hydrochloric acid and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. To the crude residue in 200 ml of methylene chloride there was added diisopropylethylamine (14.3 ml, 82.3 mmole) and triflic anhydride (10.1 ml, 60.4 mmole) at -78°C. After 1/2 hour, the mixture was poured into saturated sodium bicarbonate solution and extracted with methylene chloride. The organic layer was washed with 1N hydrochloride, brine and dried over magnesium sulfate. The organic layer was concentrated to give the vinyl triflate (21.0 g, 95%). To a

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solution of the vinyl triflate (4.67 g, 11.6 mmole) in 100 ml of methylene chloride and 100 ml of 1-methyl-2-pyrrolidinone was added phenyltrimethyltin (2.1 ml, 11.6 mmole), and palladium acetate (0.13 g, 0.58 mmole) at room temperature. After a couple of hours, the reaction
5 was poured into water and extracted with ether (3X). The organic layers were washed with water (3X), brine and dried over magnesium sulfate. After concentration and purification (MPLC, hexanes/ethyl acetate=10/1), the desired compound was isolated in 83% yield (3.2 g).

10 Step A:



20 Prepared from the intermediate obtained from Step A-1 (3.2 g, 9.66 mmole) which was dissolved in 100 ml of methanol, hydrogenated over PtO₂ at one atmosphere for a couple of hours (very slow reaction) and then a portion of Pd/C was added under hydrogen. The mixture was stirred for 72 hours and then filtered through Celite. The filtrate was concentrated under vacuum. The residue was purified by
25 MPLC (hexanes/ethyl acetate=10/1) to give the cis compound (1.9 g).

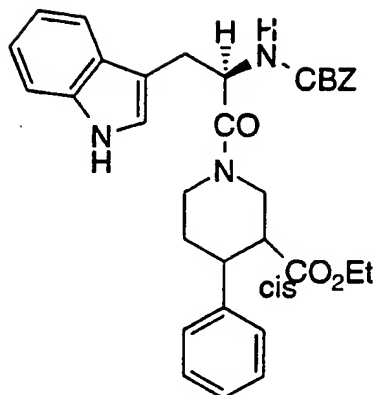
30

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Step B:

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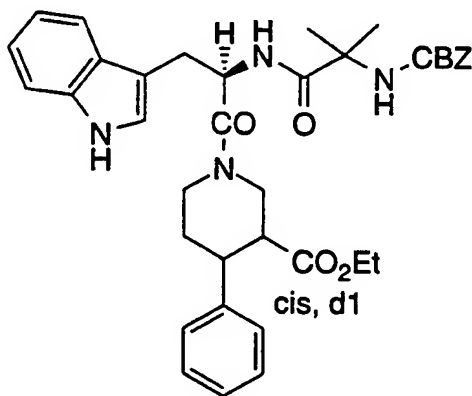
20

To intermediate prepared from Step A (200 mg, 0.6 mmole) there was added 2 ml of TFA. After 10 minutes, the mixture was concentrated and azeotroped with toluene (3X). The residue was dissolved in ethyl acetate and washed with sodium bicarbonate. The organic layer was concentrated. To the residue in 10 ml of methylene chloride there was added N-CBZ-D-tryptophan (223 mg, 0.66 mmole), EDC (138 mg, 0.72 mmole), and HOBT (89 mg, 0.66 mmole). After a couple of hours, the reaction was poured into water and extracted with methylene chloride, dried over sodium sulfate, filtered and concentrated. The residue was purified by MPLC (hexanes/ethyl acetate=2/1) to give two diastereomers in total 66% yield (the less polar diastereomer d1, 82 mg; and the more polar diastereomer d2, 138 mg).

25

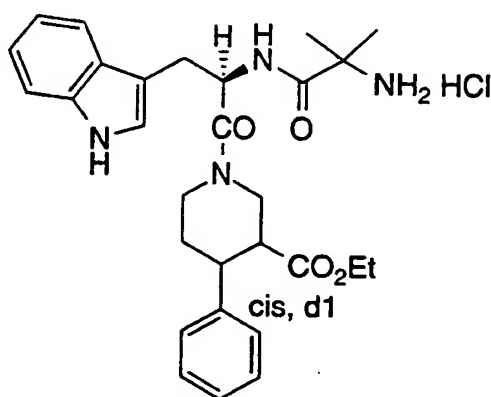
Step C:

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The less polar diastereomer from Step B (82 mg) was dissolved in 5 ml of methanol and hydrogenated over Pd/C at one atmosphere for a couple of hours (monitored by TLC). The mixture was filtered through Celite and the filtrate concentrated under vacuum. To the residue in 5 ml of chloroform was added N-CBZ-a-methylalanine (38 mg), EDC (31 mg) and HOBt (21 mg). After 3 hours stirring at room temperature, the mixture was poured into water, extracted with methylene chloride, and washed with brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by chromatatron (hexanes/ethyl acetate=1/1) to give the desired compound in 69% yield (60 mg).

Step D:

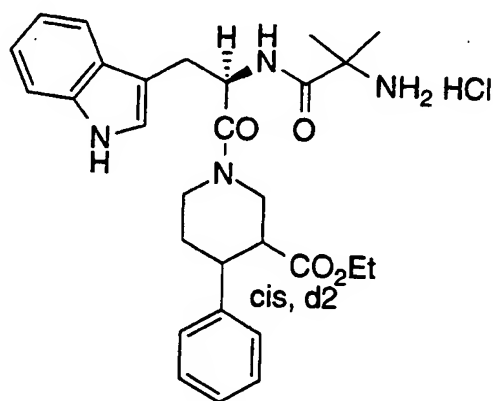
The intermediate obtained from Step C was dissolved in 3 ml of methanol and hydrogenated over Pd(OH)₂/C at one atmosphere for an hour (monitored by TLC). The mixture was filtered through Celite and the filtrate concentrated under vacuum. The residue was acidified with HCl in ether to give a white precipitate (d1, 40 mg).

¹H NMR (400 MHz, CD₃OD mixture of rotamers): 7.64 (d, 8 Hz, 1/2 H), 7.57 (d, 8 Hz, 1/2 H), 7.37-7.01 (m, 9 H), 5.28 (dd, 8, 5 Hz, 1/2 H), 5.18 (t, 7 Hz, 1/2 H), 4.76 (m, 1 H), 4.30 (m, 1/2 H), 4.15 (m, 1/2 H), 3.81 (m, 2 1/2 H), 3.35 (m, 1/2 H), 3.16 (m, 2 1/2 H), 3.02 (m, 1 1/2 H), 2.98 (m, 1/2 H), 2.45 (m, 1 H), 2.25 (m, 1/2 H), 1.74 (m, 1/2 H), 1.63 (m, 1/2 H),

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1.57 (s, 3/2H), 1.52 (s, 3/2H), 1.49 (s, 3/2H), 1.34 (s, 3/2H), 0.98 (t, 7 Hz, 3/2 H), 0.90 (t, 7 Hz, 3/2 H). FAB-MS: 505.6 (M+1).

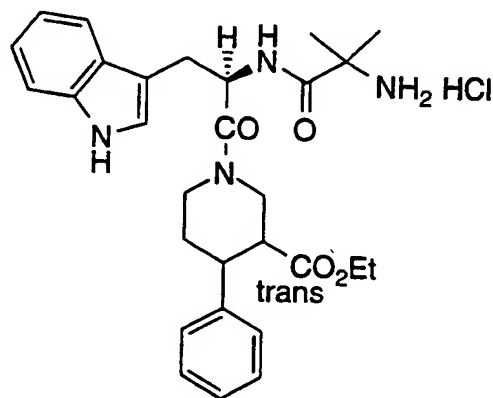
EXAMPLE B13 (cis, d2)



Prepared from the intermediate obtained from the more polar diastereomer of Example B12, Step B (93 mg) by the procedure described in Example B12 Steps C and D to give the desired compound (d2, 56 mg).

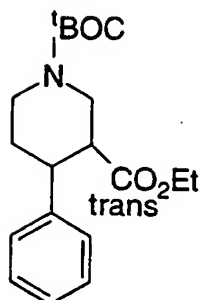
^1H NMR (400 MHz, CDCl_3 , mixture of rotamers): 7.57(m, 1 H), 7.35-6.94(m, 9 H), 5.37(t, 7 Hz, 2/3 H), 5.17 (m, 1/3 H), 4.61 (m, 1 H), 4.28 (m, 1/3 H), 4.06 (m, 2/3 H), 3.84-3.53 (m, 2 H), 3.28-2.80 (M, 5 H), 2.53 (M, 1 H), 1.61 (S, 2 H), 1.51 (S, 1 H), 1.47 (S, 2 H), 1.29 (S, 1 H), 0.95 (t, 7 Hz, 2 H), 0.80 (t, 7 Hz, 1 H). FAB-MS: 505.7.

EXAMPLE B14 (trans, d1+d2)



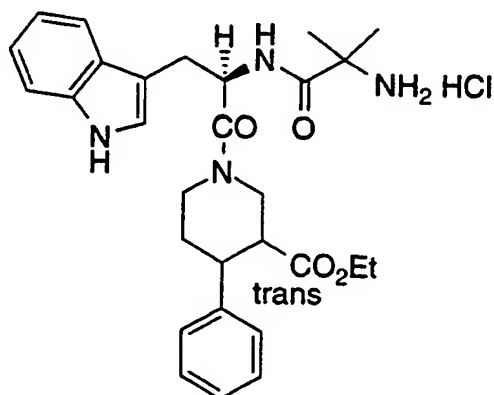
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Step A:



10 A small piece of sodium was added to 2.5 ml of anhydrous ethanol. When the sodium was dissolved, the intermediate from Example B12, Step A (40 mg) was added to the reaction mixture and placed in an 80°C oil bath for 2 hours. This mixture was poured into 0.1N HCl and extracted with ether. The organic layer was dried over 15 sodium sulfate, filtered and concentrated. The residue was purified by PLC (hexanes/ethyl acetate=5/1) to give the trans isomer (26 mg).

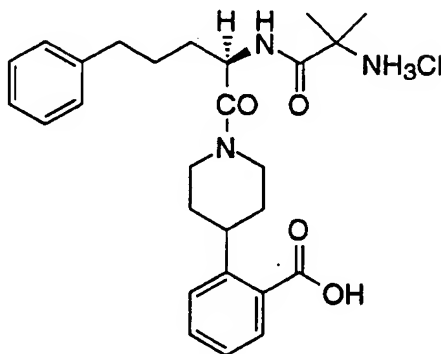
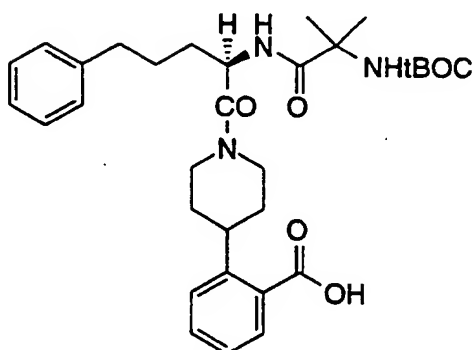
Step B:



30 Prepared from the intermediate obtained from Step A (24 mg) and Intermediate 1 according to the procedures described in Example B7, Steps B and C to give 5.4 mg of product as the hydrochloride salt. ¹H NMR (400 MHz, CD₃OD, mixture of diastereomers and rotamers): 7.63-7.35 (m, 2 H), 7.24-6.75 (m, 8 H), 5.01 (m, 1 H), 4.60 (m, 1 H), 4.08-3.68 (m, 3 1/3 H), 3.39-2.41 (m, 5 2/3 H), 1.78-0.96 (1 1/3 H), 1.62

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(s, 3 H), 1.61 (s, 3 H), 0.86 (m, 3 H), 0.66 (m, 1/3 H), -0.10 (m, 1/3 H).
FAB-MS: 505.6 (M+1).

EXAMPLE B15Step A:

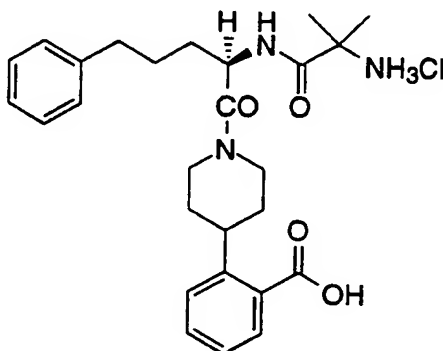
Approximately 0.250g of the piperidine intermediate prepared in Step A of Example B44 was reacted with 0.39g of Intermediate 3, 0.152g of HOBT, 0.17mL of N-methylmorpholine, and 0.225g of EDC in 15mL of chloroform for 18h. The reaction mixture was washed with 0.50N HCl (10mL), saturated aqueous NaHCO₃ (10mL), dried over MgSO₄ and concentrated. The crude was purified by flash chromatography with hexane-EtOAc (4:1) as the eluent.

To 0.136g of this material in 10mL a 1:1 mixture of methanol-water was added 25mg of lithium hydroxide and stirred overnight. The reaction mixture was diluted with 10mL of water and

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washed with water, the aqueous layer was acidified to pH=2 with 0.50 N HCl and extracted with ether (3X10mL). The combined organics were washed with brine, dried over MgSO₄ and concentrated to give the desired material as a white solid.

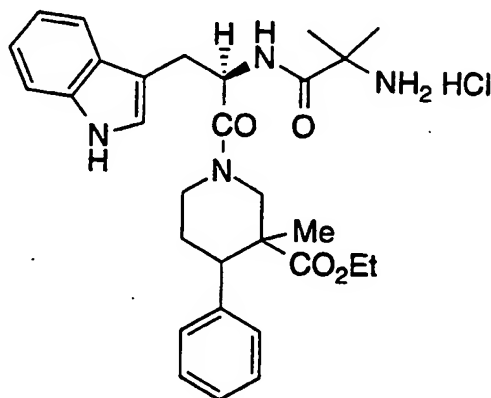
Step B:



The title compound was prepared from the compound made in Step A by treating it with a saturated solution of HCl(gas) in ethyl acetate for 30min. at RT. Ether was added and the precipitate was filtered and dried.

¹H NMR (400 MHz, CD₃OD mixture of rotamers): 8.10 (t, 1H), 7.78 (dd, 1H), 7.50-7.00 (m, 8H), 4.90 (m, 1H), 4.55 (d, 1H), 3.94 and 3.90 (2 doublets, 1H), 3.80-3.60 (m, 1H), 3.05 (dt, 1H), 2.70-2.50 (m, 4H), 1.90-1.50 (m, 6H), 1.55 (s, 3H), 1.50 (s, 3H), 1.40 (m, 1H).

EXAMPLE B16



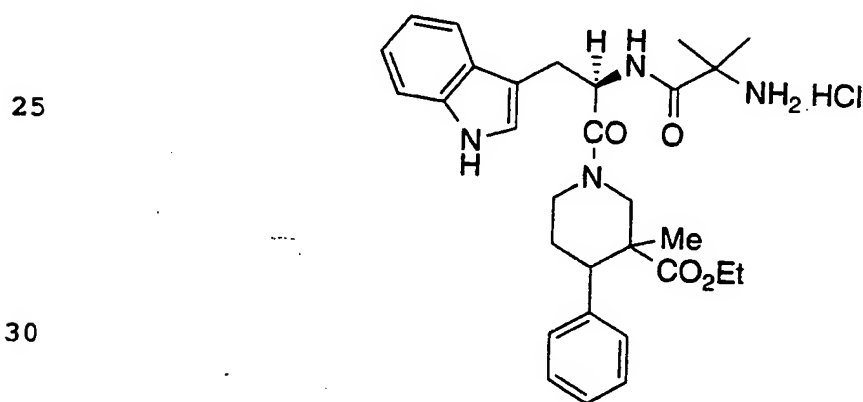
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Step A:

To a solution of the intermediate obtained from Example B12, Step A (89 mg, 0.267 mmole) in 2 ml of THF there was added potassium bis(trimethylsilyl)amide (0.5 M, 800 ml, 0.4 mmole) at -78°C . After 1/2 hour, methyl iodide (22 ml, 0.34 mmole) was added to reaction mixture. This reaction was slowly warmed up to room temperature and stirred for additional 12 hours. The mixture was poured into water and then extracted with ether. The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by a chromatatron (hexanes/ethyl acetate=1/1) to give the desired compound (91 mg, 98%).

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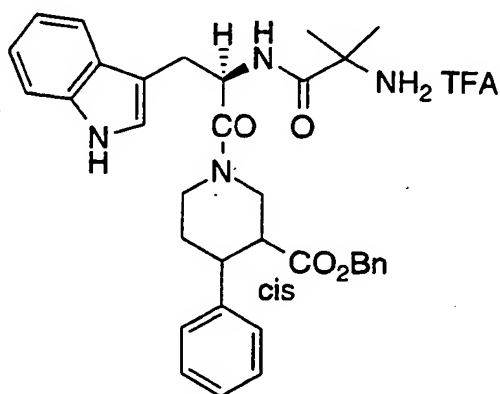
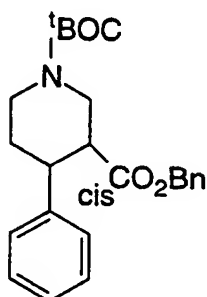
20

Step B:

Prepared from the intermediate obtained from Step A (91 mg) by the procedure described in Example B12, Steps B, C, and D to give the desired compound.

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¹H NMR (400 MHz, CD₃OD, mixture of diastereomers and rotamers):
 7.58 (m, 1 H), 7.37-7.00 (m, 9 H), 5.40-5.23 (m, 1 H), 4.60 (m, 1 H),
 4.20-3.73 (m, 3 H), 3.40 (m, 1/2 H), 3.15 (m, 2 H), 2.82 (m, 1 H), 2.61-
 2.30 (m, 2 1/2 H), 1.72 (m, 1/2 H), 1.63-1.29 (m, 6 H), 1.13-0.84 (m, 6
 H). EI-MS: 518.2 (M).

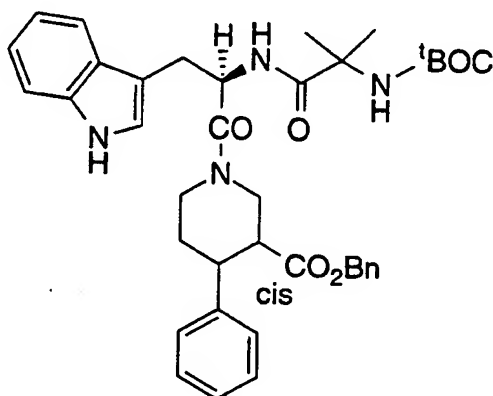
EXAMPLE B17(cis, d1+d2)Step A:

To a stirred solution of the intermediate prepared from
 Example B12. Step A-1 (1.0 g, 3.02 mmole) in 4 ml of ethanol there was
 added 4N sodium hydroxide (4 ml). The reaction was stirred at room
 temperature for 16 hours and evaporated *in vacuo*. The residue was
 diluted with water and acidified with 0.5N hydrochloric acid and then
 extracted with ether. The organic layer was dried over sodium sulfate,
 filtered and concentrated. The crude residue was dissolved in methanol
 and hydrogenated over Pd(OH)₂ at one atmosphere for 16 hours. The

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mixture was filtered through Celite and the filtrate concentrated under vacuum. To crude acid in 10 ml of chloroform there was added benzyl alcohol (341 ml), EDC (750 mg) and a catalytic amount of DMAP. After 16 hours, the mixture was diluted with methylene chloride and then washed with water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by MPLC (hexanes/ethyl acetate=5/1) to give the desired compound (459 mg, 38%).

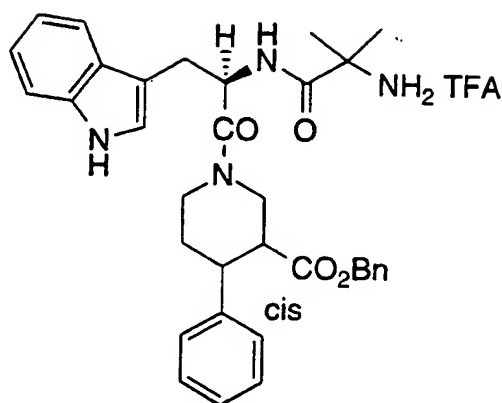
Step B:



To intermediate prepared from Step A (459 mg, 1.16 mmole) there was added 2 ml of TFA at room temperature. After 10 minutes, the reaction mixture was concentrated and azeotroped with toluene (3X). To the residue in 10 ml of chloroform there was added Intermediate 1 (433 mg), EDC (265 mg), HOBt (172 mg), and triethylamine (194 ml). The reaction was stirred at room temperature for 3 hours and poured into water. The mixture was extracted with methylene chloride, and dried over sodium sulfate. Concentration and purification (MPLC, hexanes/ethyl acetate=1.5/1) gave the coupling product (574 mg) in 76% yield.

Step C:

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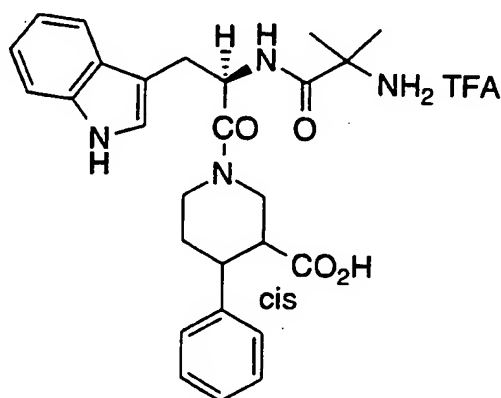


To intermediate (10 mg) obtained from Step B there was added TFA at room temperature. After 10 minutes, the mixture was concentrated to give the desired compound (3 mg).

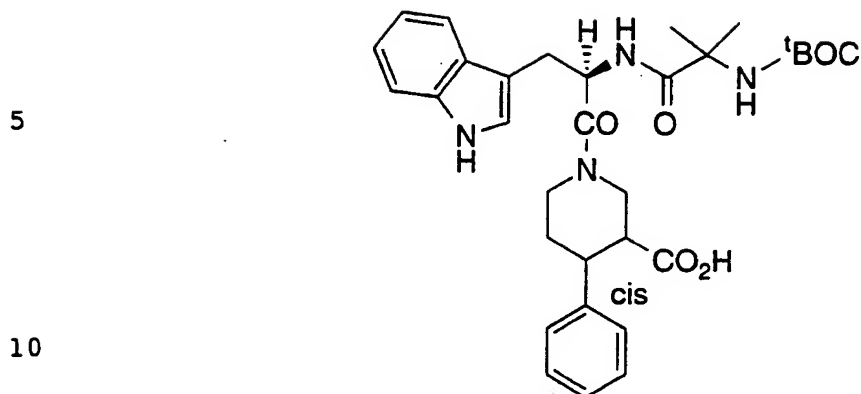
^1H NMR (400 MHz, CD_3OD , mixture of diastereomers and rotamers):

7.62 (m, 1 H), 7.37-6.81 (m, 14 H), 5.42-5.15 (m, 1 H), 4.79 (m, 2 H), 4.65 (m, 1 H), 4.32 (m, 1/2 H), 4.12 (m, 1/2 H), 3.27-2.85 (m, 5 1/2 H), 2.55-2.27 (m, 1 1/2 H), 1.74 (m, 1 H), 1.60-1.29 (m, 6 H). FAB-MS: 567.0 ($\text{M}+1$).

EXAMPLE B18 (cis,d1+d2)

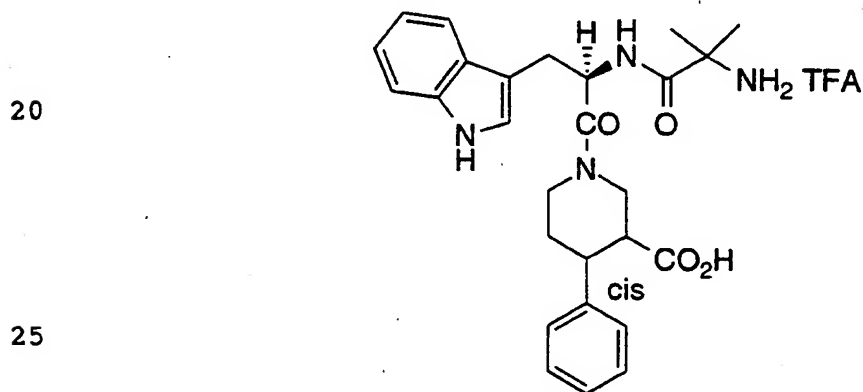


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Step A:

Prepared from the intermediate obtained from Example B17, Step B (20 mg) by the procedure described in Example B8 to give the desired compound.

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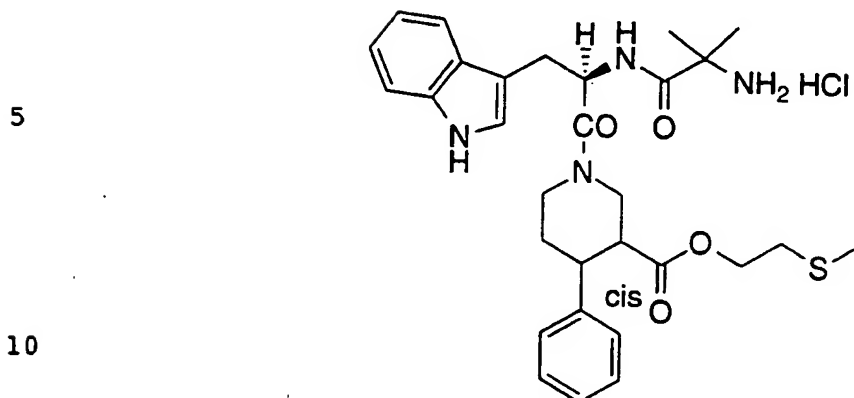
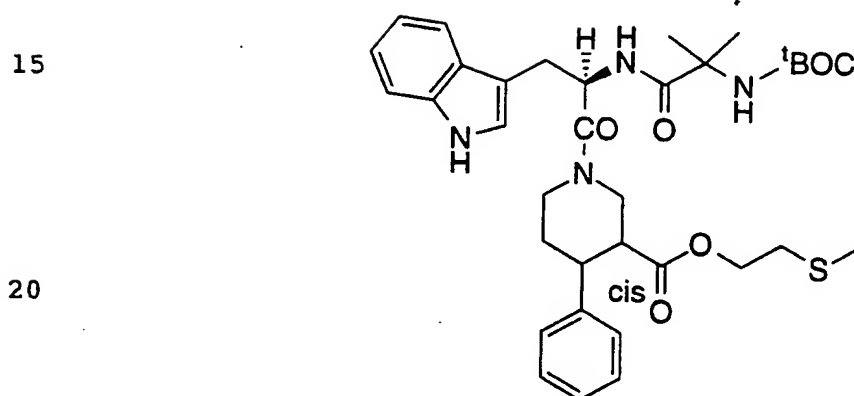
Step B:

Prepared from the intermediate obtained from Step A by the procedure described in Example B17, Step C to give the desired compound (10 mg).

30

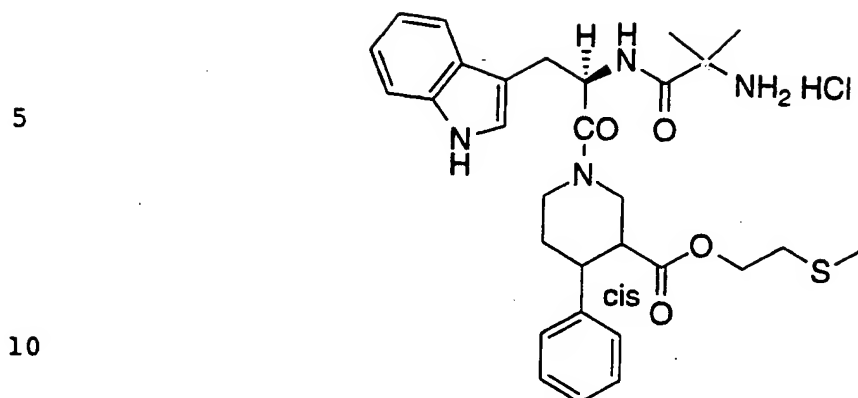
¹H NMR (400 MHz, CD₃OD, mixture of diastereomers and rotamers): 7.62 (m, 1 H), 7.37-6.98 (m, 9 H), 5.36-5.21 (m 1 H), 4.69 (m, 1/2 H), 4.58 (m, 1/2 H), 4.27-3.91 (m, 2 H), 3.27-2.75 (m, 5 H), 2.51-2.34 (m, 2 H), 1.72 (m, 1 H), 1.58-1.21 (m, 6 H). FAB-MS: 576.9 (M+1).

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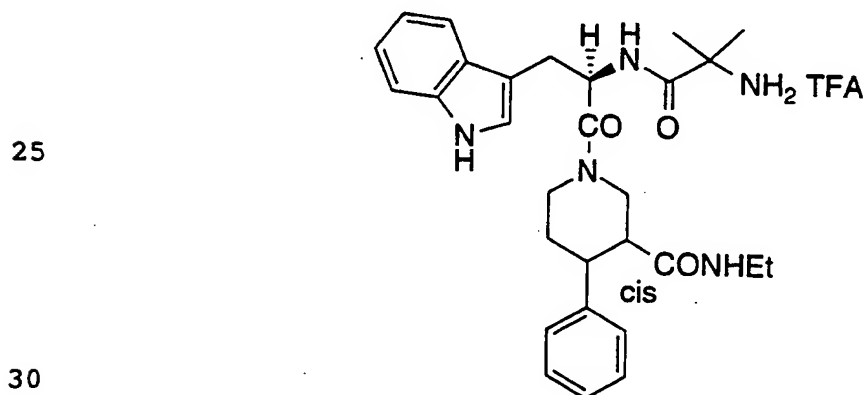
EXAMPLE B19 (cis, dl+d2)Step A:

Prepared from the intermediate obtained from Example B18,
25 Step A (142 mg) in 3 ml of methylene chloride to which there was added
2-(methylthio)ethanol (22 ml), EDC (57 mg) and a catalytic amount of
DMAP. After 3 hours, the mixture was diluted with methylene chloride
and then washed with water and brine. The organic layer was dried over
magnesium sulfate, filtered and concentrated. The residue was purified
30 by PLC (hexanes/ethyl acetate=1/1) to give the desired product (69 mg,
43%).

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Step B:

Prepared from the intermediate obtained from Step A (50 mg) in 2 ml of ether into which there was bubbled HCl gas at 0°C. After 30 seconds, the mixture was concentrated to give the white solid (41 mg).
 15 ¹H NMR (400 MHz, CD₃OD, mixture of diastereomers and rotamers):
 7.61(m, 1 H), 7.37-6.97 (m, 9 H), 5.38-5.18 (m 1 H), 4.83-4.54 (m, 1 H),
 4.37-3.77 (m, 3 H), 3.57-2.83 (m, 6 H), 2.55-2.21 (m, 3 H), 2.14-1.84 (m,
 3 H), 1.72 (m, 1 H), 1.61-1.29 (m, 6 H). FAB-MS: 551.0 (M+1).

EXAMPLE B20 (cis, d1+d2)

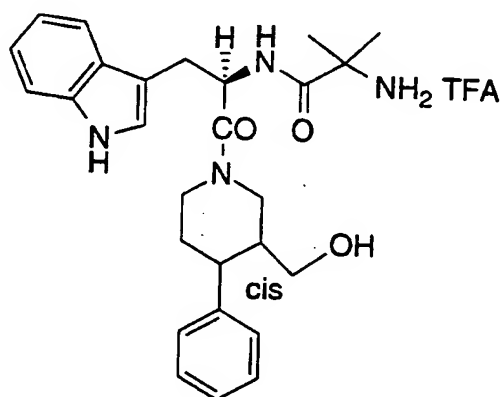
Prepared from the intermediate obtained from Example B18, Step A (52 mg) in 3 ml of methylene chloride to which there was added ethylamine hydrochloride (9 mg), EDC (21 mg), triethylamine (15 ml) and a catalytic amount of DMAP. After 3 hours, the mixture was diluted

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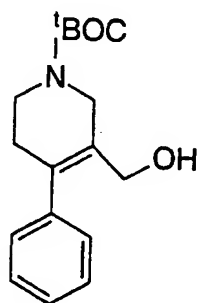
with methylene chloride and then washed with water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by PLC (methylene chloride/methanol=20/1) to give the coupling product (25 mg). This intermediate by the procedure described in Example B17, Step C gave the desired compound (25 mg).

¹H NMR (400 MHz, CD₃OD, mixture of diastereomers and rotamers): 7.68-6.93 (m, 10 H), 5.34-5.12 (m, 1 H), 4.75-4.30 (m, 2 H), 3.50-2.60 (m, 8 H), 1.72-1.17 (m, 8 H), 0.83-0.68 (m, 3 H). FAB-MS: 504.0 (M+1).

EXAMPLE B21 (cis, d1+d2)



Step A:

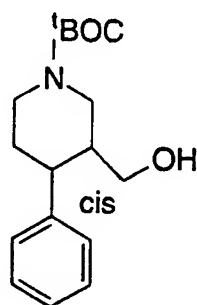


To a solution of the intermediate obtained from Example B12, Step A-1 (950 mg, 2.87 mmole) in 10 ml of THF there was added diisobutylaluminum hydride (1.0 N in methylene chloride, 8 ml, 8.0

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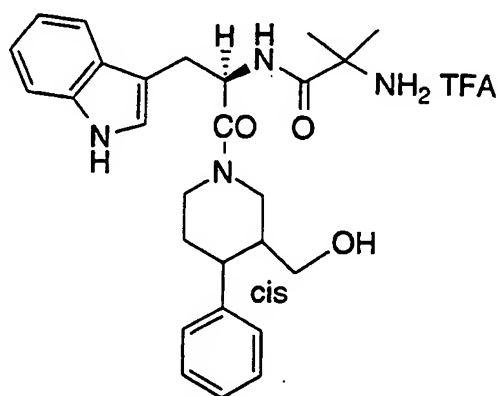
mmole) at -78°C . The mixture was stirred at 0°C for 1 hour and then slowly warmed to room temperature. The mixture was quenched with 1N sodium hydroxide, and extracted with ether (3X). The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by MPLC (hexanes/ethyl acetate=2/1) to give 617 mg of reduction product.

Step B:



Prepared from the intermediate obtained from Step A (57 mg) by hydrogenation under the conditions described in Example B12, Step A to give the desired compound (13 mg).

Step C:

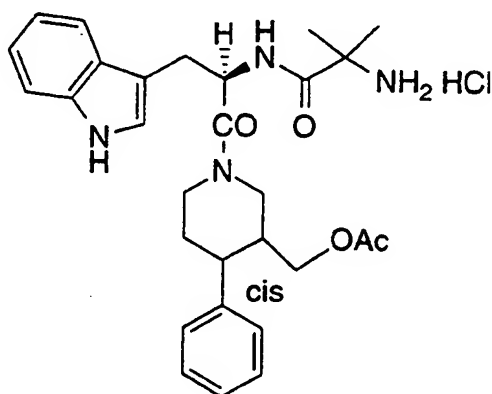


Prepared from the intermediate obtained from Step B (13 mg) by the procedure described in Example B17, Steps B and C to give the desired compound (12 mg).

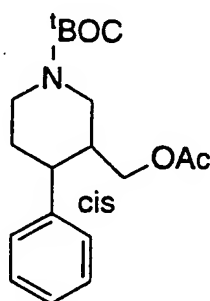
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¹H NMR (400 MHz, CD₃OD, mixture of diastereomers and rotamers):
7.74-6.80 (m, 10 H), 5.55 (m 1/2 H), 5.20 (m, 1/2 H), 4.66(m, 1 H), 4.11
(m, 1/2 H), 3.93 (m, 1/2 H), 3.20 (m, 3 H), 3.00-2.82 (m, 2 1/2 H), 2.69-
2.45 (m, 2 1/2 H), 2.05-1.84 (m, 1 H), 1.68 (s, 3/2 H), 1.61 (s, 3/2 H),
1.60 (s, 3/2 H), 1.47 (s, 3/2 H), 0.90 (m, 1/2 H), 0.17 (m, 1/2 H). FAB-
MS: 463.0 (M+1).

EXAMPLE B22 (cis, d1+d2)



Step A:

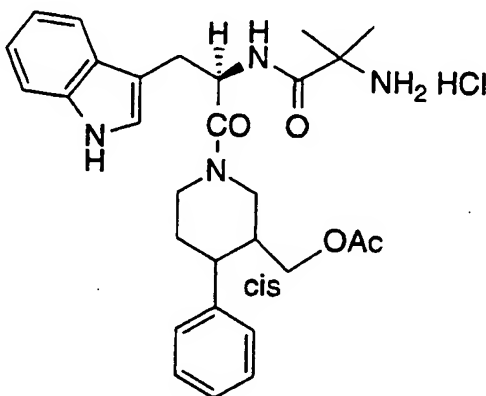


Prepared from the intermediate obtained from Example B21,
Step A (330 mg, 1.14 mmole) in 10 ml of methylene chloride to which
there was added acetic anhydride (130 ml), triethylamine (240 ml), and a
catalytic amount of DMAP at 0°C. After 1 hour, water was added to the
mixture and it was stirred an additional 1 hour at room temperature. The
mixture was extracted with methylene chloride and then washed
sequentially with 1N sodium hydroxide and brine. The organic layer was

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dried over magnesium sulfate, filtered and concentrated. The residue was hydrogenated under the conditions described in Example B12, Step A to give the desired compound.

5 Step B:

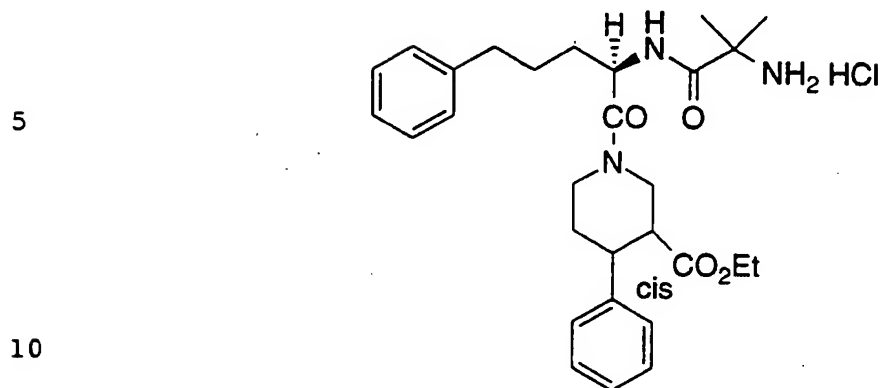
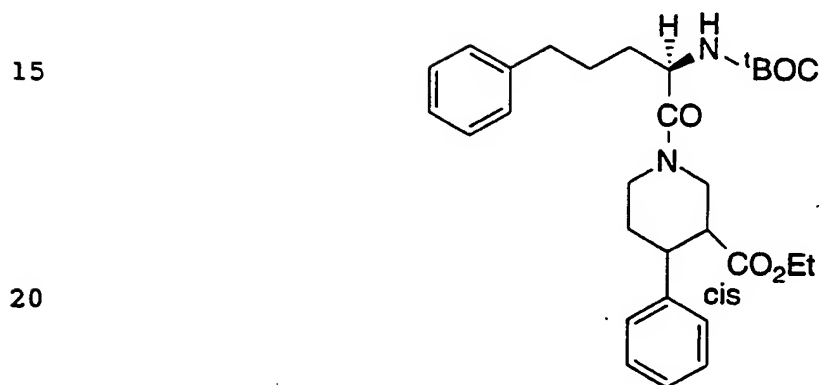


Prepared from the intermediate obtained from Step A (24 mg) by the procedure described in Example B17, Step B and Example B19, Step B to give the desired compound (23 mg).

¹H NMR (400 MHz, CD₃OD, mixture of diastereomers and rotamers):
20 7.74-6.87 (m, 10 H), 5.55-5.16 (m, 1 H), 4.65 (m, 1 H), 3.96 (m, 1 H),
3.81 (m, 1/2 H), 3.20 (m, 3 H), 2.86 (m, 1 H), 2.61 (m, 1 H), 2.46 (m, 1/2
H), 2.27 (m, 1/2 H), 2.13 (m, 1 H), 1.98 (s, 1/2 H), 1.93 (s, 1 H), 1.90 (s,
1 H), 1.85 (s, 1/2 H), 1.73-1.30 (m, 7 1/2 H), 0.85 (m, 1/2 H), 0.12 (m, 1/2
25 H). FAB-MS: 505.3 (M+1).

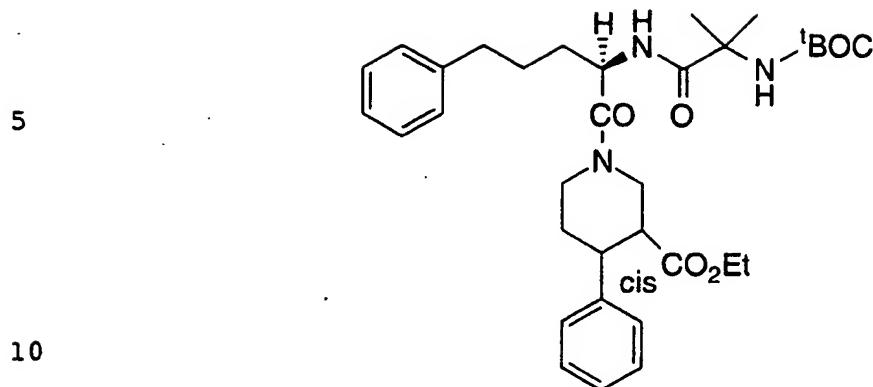
30

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EXAMPLE B23 (cis, d1)Step A:

To intermediate prepared from Example B12, Step A (87 mg) there was added 1 ml of TFA. After 10 minutes, the mixture was concentrated and azeotroped with toluene (3X). The residue was dissolved in ethyl acetate and washed with sodium bicarbonate. The organic layer was concentrated. To the residue in 3 ml of methylene chloride there was added N-BOC-(2R)-amino-5-phenylpentanoic acid (70 mg), EDC (55 mg), and HOBt (35 mg). After a couple of hours, the reaction was poured into water and extracted with methylene chloride, dried over sodium sulfate, filtered and concentrated.

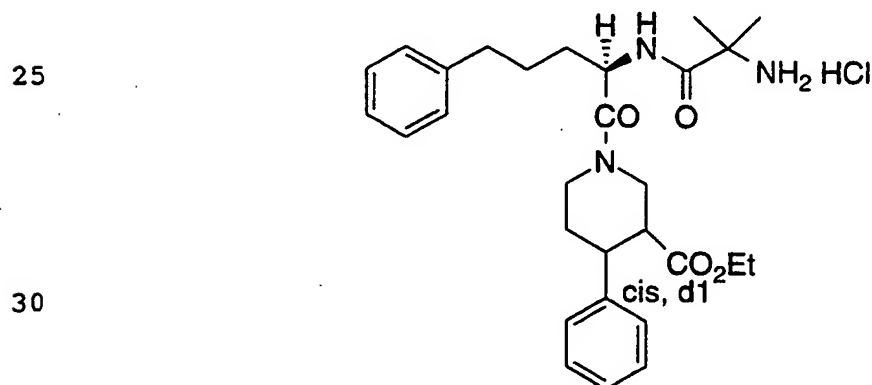
- 175 -

Step B:

To intermediate prepared from Step A there was added 1 ml of TFA. After 10 minutes, the mixture was concentrated and azeotroped with toluene (3X). To the residue in 3 ml methylene chloride there was added BOC-a-methylalanine, EDC, HOBt, and triethylamine. After a couple of hours, the reaction was poured into water and extracted with methylene chloride, dried over sodium sulfate, filtered and concentrated. The residue was purified by MPLC (hexanes/ethyl acetate=2/1) to give two diastereomers in 75% yield (the less polar diastereomer d1, 54 mg; the more polar diastereomer d2, 53 mg).

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Step C:

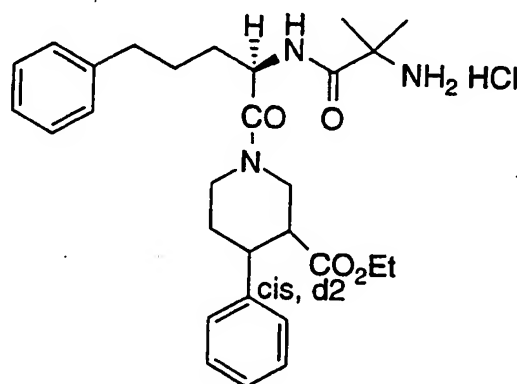
To the less polar diastereomer prepared from Step B (54 mg) was added 1 ml of TFA. After 10 minutes, the mixture was concentrated

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and azeotroped with toluene (3X). The residue was dissolved in ethyl acetate and washed with sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was dissolved in ether to which was added HCl in ether to give a white solid (d1, 40 mg).

¹H NMR (400 MHz, CD₃OD mixture of rotamers): 7.23 (m, 10 H), 5.08 (m, 1 H), 4.76 (m, 1 H), 4.21 (m, 1 H), 3.80 (m, 2 1/2 H), 3.47 (m, 1/2 H), 3.26-2.99 (m, 4 H), 2.86 (m, 1/2 H), 2.63 (m, 2 H), 2.40 (m, 1/2 H), 1.75 (m, 4 H), 1.63 (s, 2 H), 1.60 (s, 2 H), 1.57 (s, 2 H), 0.95 (t, 7 Hz, 2 H), 0.87 (t, 7 Hz, 1 H). FAB-MS: 494.1 (M+1).

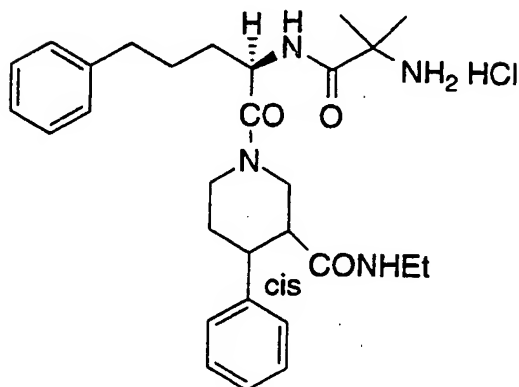
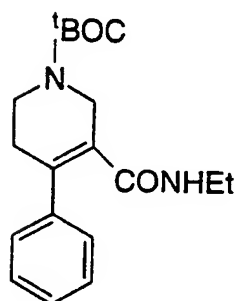
EXAMPLE B24 (cis, d2)



The desired d2 compound (40 mg) was prepared from the more polar diastereomer obtained in Example B23, Step B (53 mg) by the procedure described in Example B23, Step C.

¹H NMR (400 MHz, CD₃OD mixture of rotamers): 7.23 (m, 10 H), 4.91 (m, 1 H), 4.75 (m, 1 H), 4.03 (m, 1 H), 3.81 (m, 2 H), 3.45 (m, 1/2 H), 3.26-2.96 (m, 4 H), 2.71 (m, 2 1/2 H), 2.40 (m, 1 H), 1.90-1.64 (m, 4 H), 1.63 (s, 2 H), 1.61 (s, 3 H), 1.59 (s, 3 H), 0.93 (t, 7 Hz, 3 H). FAB-MS: 494.3 (M+1).

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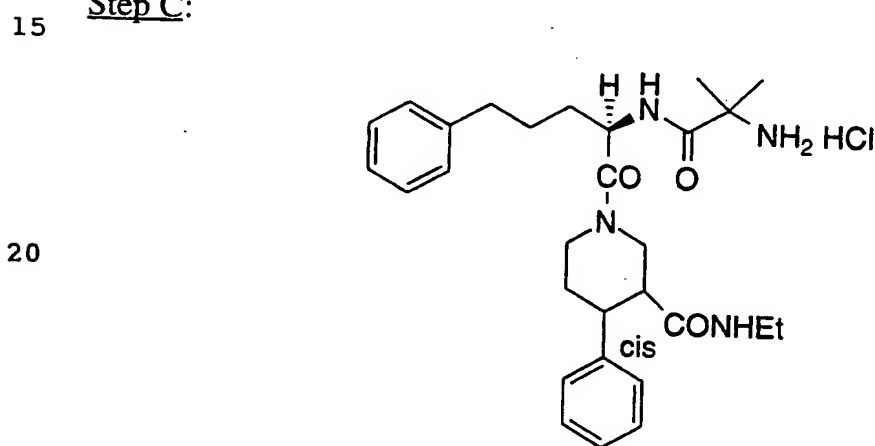
EXAMPLE B25 (cis, d1+d2)Step A:

To a stirred solution of the intermediate prepared from Example B12, Step A-1 in 4 ml of ethanol there was added 4N sodium hydroxide (4 ml). The reaction was stirred at room temperature for 16 hours and evaporated *in vacuo*. The residue was diluted with water and acidified with 0.5N hydrochloric acid and then extracted with ether. The organic layer was dried over sodium sulfate, filtered and concentrated. The residue (100 mg) in 3 ml of methylene chloride there was added ethylamine hydrochloride (74 mg), EDC (115 mg), HOBt (49 mg) and triethylamine (83 ml). After a couple of hours, the reaction was poured into water and extracted with methylene chloride, dried over sodium sulfate, filtered and concentrated. The residue was purified by MPLC (hexanes/ethyl acetate=1/1) to give desired compound (74 mg).

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Step B:

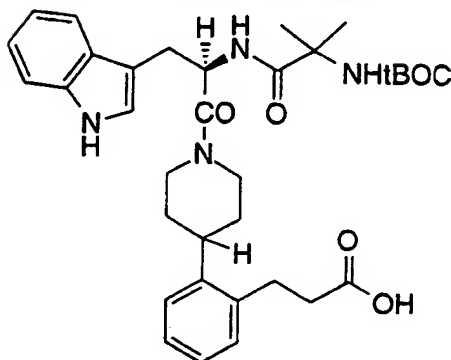
Prepared from the intermediate obtained from Step A (74 mg) by the procedure described in Example B12, Step A to give desired compound (60 mg).

Step C:

25 Prepared from the intermediate obtained from Step B (60 mg) by the procedure described in Example B23, Steps A, B, and C to give the desired compound (15 mg).

¹H NMR (400 MHz, CD₃OD mixture of diastereomers and rotamers):
 30 7.27 (m, 10 H), 4.91 (m, 1 H), 4.67 (m, 1 H), 3.96 (m, 1 H), 3.42 (m, 1/2 H), 3.26-2.59 (m, 9 1/2 H), 1.90-1.64 (m, 4 H), 1.64-1.57 (m, 6 H), 0.79 (t, 7 Hz, 3/2 H), 0.77 (t, 7 Hz, 3/2 H). FAB-MS: 493.3 (M+1).

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INTERMEDIATE 4

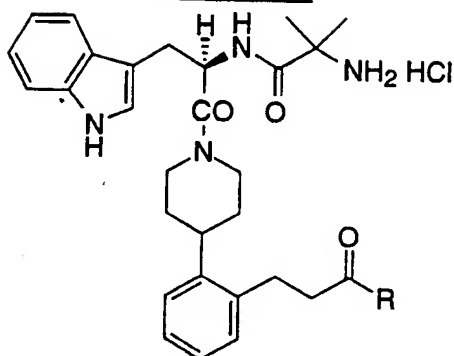
To a solution of 0.80g of the compound prepared in Step B of Example B7 in 20mL of ethanol was added 0.080g of 20% pallium hydroxide/C and hydrogenated at atmospheric pressure for 3h. The catalyst was filtered through a pad of celite and the filtrate was concentrated to give the title compound.

EXAMPLES B26, B27, B28, B29

The following compounds shown in Table B1 were prepared in two steps from Intermediate 4. The acid intermediate in a methylene chloride solution was coupled with alcohols or amines in the presence of EDC and DMAP at ambient temperature and these intermediates were purified and treated with hydrochloric acid(gas) in ethyl acetate to provide the compounds shown in Table B1.


- 180 -

TABLE B1



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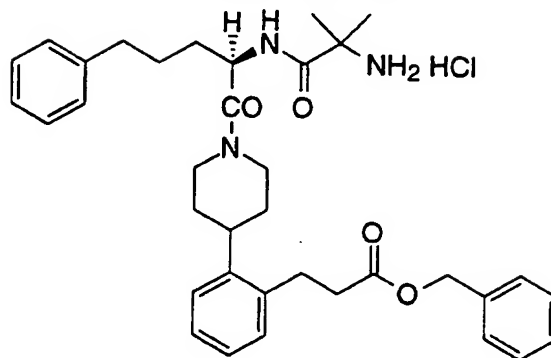
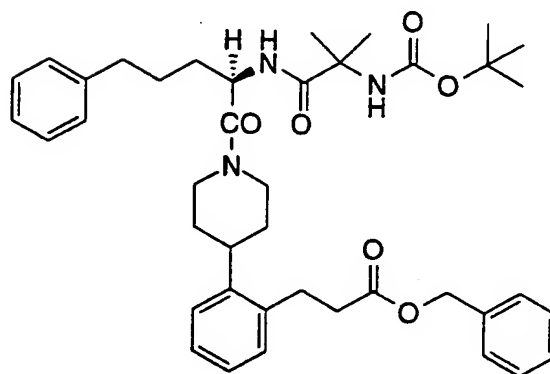
| Example No. | R | molecular formula | FAB MS m/e calc. | m/e found (m+1) |
|-------------|---|---|---------------------|--------------------|
| B26 | OCH(CH ₃) ₂ | C ₃₁ H ₄₂ N ₄ O ₄ | 569 | 570.2 |
| B27 | O(CH ₂) ₃ CH ₃ | C ₃₃ H ₄₄ N ₄ O ₄ | 560 | 561.1 |
| B28 |  | C ₃₃ H ₄₃ N ₅ O ₄ | 573.33 | 574.1 |
| B29 | NHCH ₂ CH ₃ | C ₃₁ H ₄₁ N ₅ O ₃ | 531 | 532.3 |

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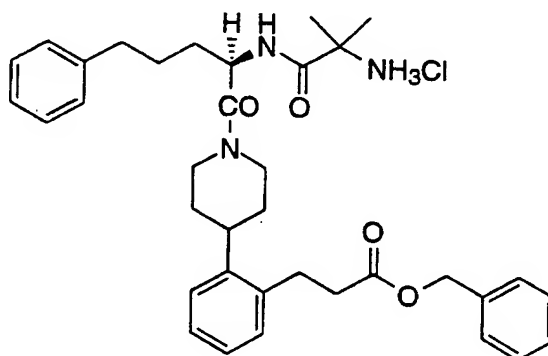
EXAMPLE B30Step A:

To a solution of 1.1g of the piperidine intermediate prepared in Example B7, Step A in 5mL of ethyl acetate at room temperature was bubbled in HCl (gas) for 10 seconds and stirred for 30 min. The solvent was removed and the oily residue was basified with aqueous sodium bicarbonate solution and extracted with CH₂Cl₂. The combined organics were washed with brine, dried over K₂CO₃, filtered, and concentrated to give 0.90g of the amine as a thick oil. To a solution of the above intermediate in 20mL of CH₂Cl₂ was added 0.97g of (2R)-N-t-BOC-5-phenylpentanoic acid, 0.45g of HOBT, and 0.80g of EDC and stirred at RT overnight. The reaction mixture was poured into saturated aqueous sodium bicarbonate solution and extracted with CH₂Cl₂. The combined organics were washed with 0.50N hydrochloric acid solution, brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography with hexane-acetone (5:1) as the eluent to yield about 2.0g of the coupled product.

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The above intermediate was treated with 2mL of trifluoroacetic acid in 20mL of CH₂Cl₂ at room temperature for 1h. The volatiles were removed on the rotary evaporator and the residue was basified with aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined organics were dried over K₂CO₃, filtered and concentrated. The residue was dissolved in CH₂Cl₂ and coupled with 0.60g of N-t-BOC- α -methylalanine in the presence of 0.40g of HOBT and 0.70g of EDC. The reaction was stirred overnight and worked up as described above. The residue was purified by flash chromatography using hexane-acetone (5:1) as the eluent to give the title compound as a colorless foam.

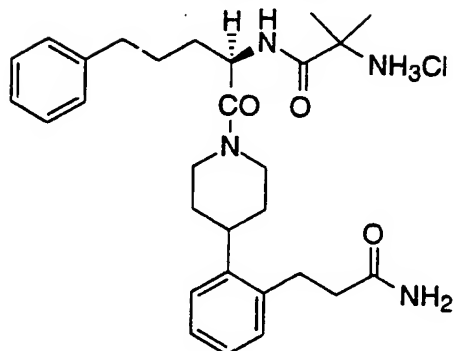
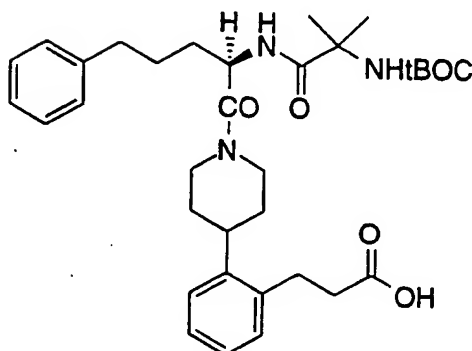
¹H NMR (400 MHz, CDCl₃ mixture of rotamers): 7.40-6.85 (m, 14 H), 5.10 (s, 2H), 5.05-4.88 (m, 2H), 4.70-4.60 (m, 1H), 3.93 (d, 1/2H), 3.85 (d, 1/2H), 3.10-2.85 (m, 4H), 2.70-2.50 (m, 5H), 1.85-1.60 (m, 7H), 1.50 (s, 3H), 1.48 and 1.47 (2s, 3H), 1.42 (s, 9H), 1.40-1.20 (m, 1H).

Step B:

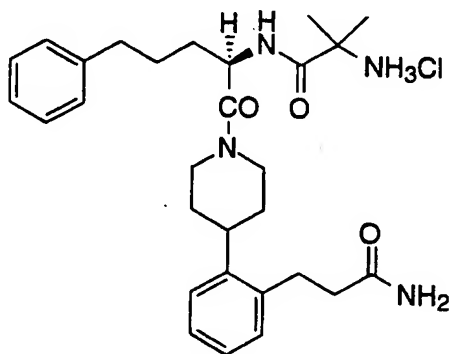
Approximately 0.050g of the intermediate from Step A was dissolved in 1mL of ethyl acetate and 1mL of saturated HCl(gas) in ethyl acetate was added and stirred for at room temperature for 30min. The reaction mixture was cooled to 0°C and ether was added and the solvents were evaporated to leave the derived product as a foam.

¹H NMR (400 MHz, CD₃OD mixture of rotamers): 7.40-7.00 (m, 14H), 5.10 (s, 2H), 4.90 (m, 1H), 4.58 (d, 1H), 3.95 and 3.90 (2 doublets, 1H), 3.20-2.95 (m, 4H), 2.80-2.60 (m, 5H), 1.85-1.60 (m, 9H), 1.62 (s, 3H), 1.60 (s, 1H), 1.40 (m, 1H).

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EXAMPLE B31Step A:

To 0.90g of the intermediate prepared in Step A Example B30 in 5mL of methanol was added 0.10g of 20% palladium hydroxide and hydrogenated at atmospheric pressure overnight. The catalyst was filtered off through a pad of celite and washed with methanol. The filtrate was concentrated and the residue was dried under vacuum to provide the acid as a colorless foam that was used without purification.

Step B:

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To a solution of 0.30g of the acid intermediate prepared in Step A in 10mL of dry THF was added 0.14mL of triethylamine and 0.07mL of ethylchloroformate and stirred for 1h. The reaction was quenched with 2mL of aqueous ammonium hydroxide solution and extracted with CH₂Cl₂. The combined organics were washed with 0.50N hydrochloric acid, dried over MgSO₄ and concentrated. The residue was purified by flash chromatography with chloroform-methanol (95:5) as the eluent to provide a solid that was deprotected with HCl in ethyl acetate as described above to give the title compound as a white solid.

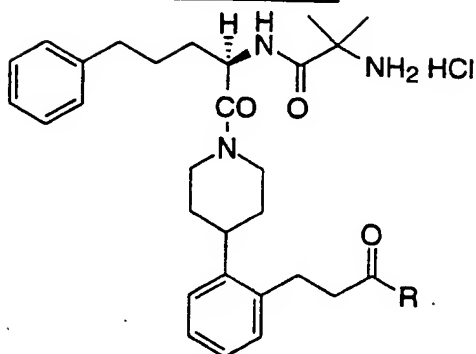
¹H NMR (400 MHz, CD₃OD mixture of rotamers): 8.15 (t, 1H), 7.30-7.00 (m, 9H), 4.90 (m, 1H), 4.70 (d, 1H), 4.05 and 3.95 (2 doublets, 1H), 3.30-2.95 (m, 4H), 2.90-2.60 (m, 3H), 2.50 (bs, 2H), 1.90-1.65 (m, 7H), 1.60 (2 singlets, 6H), 1.48 (m, 1H).

EXAMPLES 32-35 and 49

The compounds described in Table B2 were prepared from intermediate synthesized in Step A of Example B31 by taking advantage of chemistry used to prepare the title compound in Example B5. Other amines as depicted below were used in place of ethanolamine and the final deprotection was carried in ethyl acetate and dry hydrochloric acid. Ether was generally used to precipitate the hydrochloride salt.

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TABLE B2



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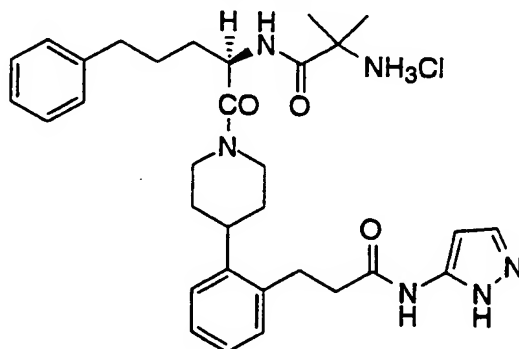
20

| Example No. | R | molecular formula | FAB MS m/e calc. | m/e found (m+1) |
|-------------|-----------------------------------|---|---------------------|--------------------|
| B32 | N(CH ₃) ₂ | C ₃₁ H ₄₄ N ₄ O ₃ | 520 | 521.2 |
| B33 | NHtBu | C ₃₃ H ₄₈ N ₄ O ₃ | 548 | 549.2 |
| B34 | | C ₃₃ H ₄₆ N ₄ O ₃ S | 578 | 579.2 |
| B49 | NHCH ₂ CH ₃ | C ₃₁ H ₄₄ N ₄ O ₃ | 520 | 521.2 |

EXAMPLE B35

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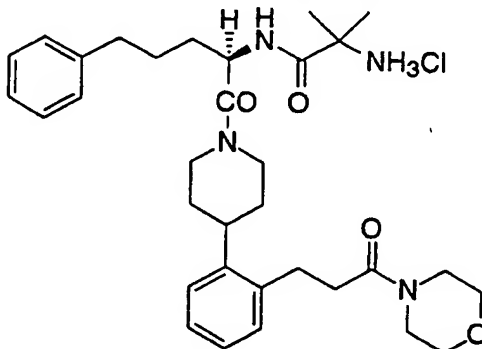
To a solution of 0.50g of the acid intermediate prepared in Step A of Example B31 in 5mL of 1,2-dichloroethane was added 0.16g of carbonyldiimidazole and stirred at 60°C for 30min. The reaction was

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cooled to RT, half of it was then treated with 0.12g of 2-aminopyrazole and heated at 60°C for 1h, cooled to RT and stirred for 2 days. The reaction mixture was poured into 0.50N aqueous hydrochloric acid and extracted with CH₂Cl₂. The combined organics were washed with brine, dried over MgSO₄, concentrated and the residue was purified by flash chromatography with hexane-acetone (1:1) as the eluent. The purified material was deprotected with the HCl/EtOAc protocol as described above to give the title compound as a white solid.

FAB MS m/e calcd. (for C₃₂H₄₂N₆O₃) 558; found 559.2 (m+1)

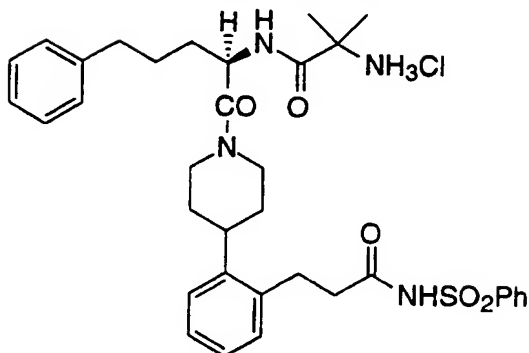
EXAMPLE B36



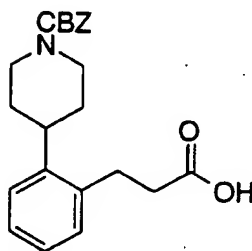
The title compound was prepared as described in Example B5 but morpholine was used in place of ethanolamine.

¹H NMR (400 MHz, CD₃OD mixture of rotamers): 7.30-6.95 (m, 9H), 4.95 (m, 1H), 4.68 (d, 1H), 4.00 and 3.95 (2 doublets, 1H), 3.59 (m, 4H), 3.35 (m, 4H), 3.25-2.90 (m, 4H), 2.80-2.50 (m, 5H), 1.90-1.65 (m, 7H), 1.63 (s, 3H), 1.60 (s, 3H), 1.47 (m, 1H).

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EXAMPLE B37

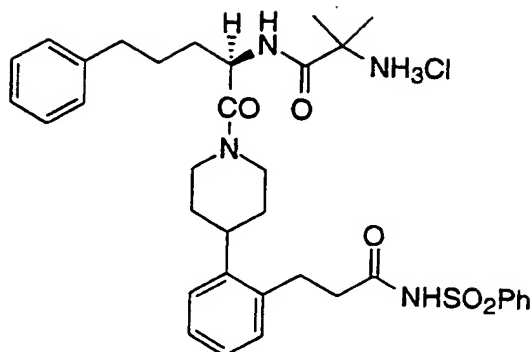
10

Step A:

To a stirred solution of 5.0g of the piperidine intermediate prepared in Example B1 Step B was added 5mL of triethylamine at 0°C and 2.8mL of CBZ-Cl. The reaction was allowed to warm up to Rt and stir overnight. The reaction mixture was poured into aqueous ammonium chloride solution and extracted with CH₂Cl₂. The organic layer was washed with 0.50N HCl solution, dried over MgSO₄ and concentrated. This crude residue was dissolved in 25 mL of methanol-water and 3eq. of sodium hydroxide was added and stirred for 2h. The reaction mixture was acidified to pH=2 with 2N HCl and extracted with EtOAc. The combined organics were washed with brine, dried over Na₂SO₄ and concentrated to give the acid as a foam.

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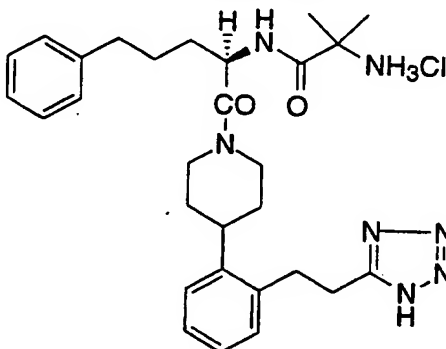
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Step B:

To a solution of 0.225g of the above acid intermediate in 10mL of CH_2Cl_2 was added 0.12g of benzenesulfonamide, 0.093g of DMAP and 0.164g of EDC and stirred overnight. The reaction mixture was washed with 0.50N HCl (2X10mL), dried over Na_2SO_4 and concentrated. The crude residue was dissolved in 10mL of methanol and 0.10g of 10% Pd/C and hydrogenated at 40psi overnight. The catalyst was filtered off through a pad of celite and the filtrate was concentrated to provide the piperidine that was used without purification.

The piperidine intermediate was now coupled to Intermediate 3 and deprotected with HCl/EtOAc as described above to give the title compound as a white solid.

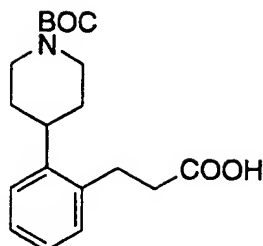
FAB MS m/e calcd. (for $\text{C}_{35}\text{H}_{44}\text{N}_4\text{O}_5\text{S}$) 632; found 633.1 (m+1)

EXAMPLE B38

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Step A:

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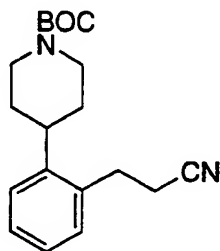


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This intermediate was prepared as described in Step A of Example B37 but di-*t*-butylcarbonate was used in place of CBZ-Cl.

Step B:

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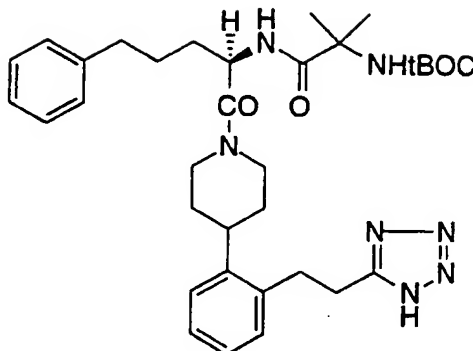


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To a stirred solution of 2.90g of the acid prepared in Step A in 30mL of dry THF was added 2.5mL of triethylamine and 1.25mL of ethylchloroformate and stirred for 30 min. 10mL of the reaction mixture was removed. The remaining mixture was quenched with 20mL of aqueous ammonium hydroxide solution, stirred for 30 min., and extracted with EtOAc. The combined organics were washed with 0.50N HCl, brine, dried over Na₂SO₄, filtered and evaporated to give an oily residue. This material was dissolved in 20mL of CH₂Cl₂ and 20mL of pyridine at 0°C and 1.1mL of POCl₃ was added and stirred for 30min. The reaction mixture was poured into brine and washed with 0.50N HCl solution, saturated NaHCO₃ solution, brine, dried over Na₂SO₄ and concentrated. Flash chromatography of the residue with hexane-ethyl acetate (5:1) as the eluent gave the desired product.

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Step C:

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To a solution of 1.0g of the nitrile intermediate prepared in Step B in 20mL of toluene was added 1.96g of trimethyltin azide and heated at reflux for 18h. The excess azide that precipitated upon cooling to room temperature was filtered off. The filtrate was concentrated and spilt in half. To this half was added 10mL of EtOAc and a trace of methanol and HCl(gas) was bubbled in for 5 minutes and stirred for 1h. Ether was added and concentrated to give a gummy material that was washed with ether and dried under vacuum to give a brownish solid. 400MHz NMR (CD₃OD) revealed that this was the desired tetrazole intermediate.

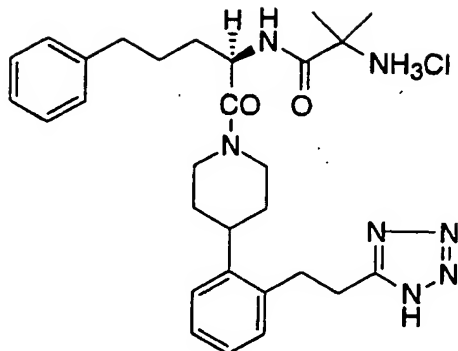
20

To 0.30g of the piperidine hydrochloride synthesized above in 10mL of chloroform was added 0.47g of Intermediate 3, 0.16g of HOBT, 0.45mL of N-methylmorpholine, and 0.29g of EDC and stirred overnight. The reaction mixture was poured into 0.50N HCl solution and extracted with CHCl₃. The combined organics were washed with brine, dried over Na₂SO₄, and concentrated to give a gummy residue that was purified by flash chromatography with CHCl₃-MeOH-NH₄OH (85:15:1) as the eluent. This provided 0.15g of the desired product.

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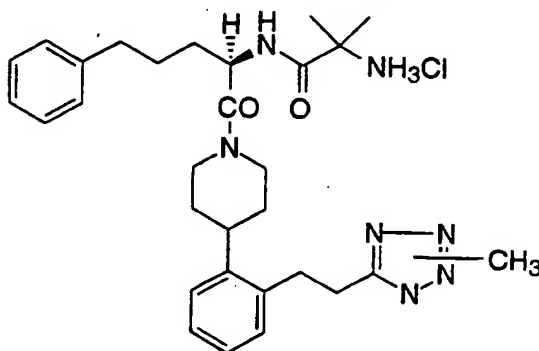
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Step D:

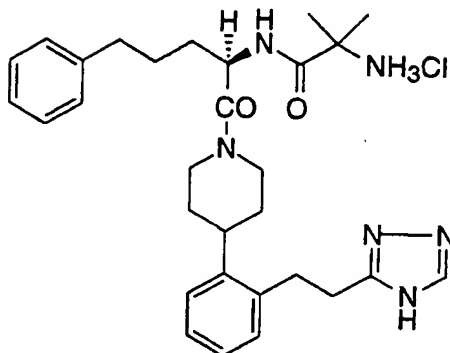
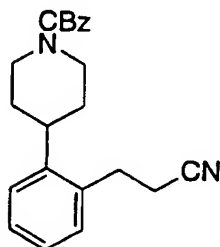
This material was prepared from the intermediate prepared in Step C by the EtOAc/HCl protocol described above.

¹H NMR (400 MHz, CD₃OD mixture of rotamers): 8.15 (t, 1H), 7.60-7.05 (m, 9H), 4.90 (m, 1H), 4.60 (d, 1H), 4.05 and 3.95 (2 doublets, 1H), 3.30-3.10 (m, 4H), 3.10-2.60 (m, 5H), 1.90-1.65 (m, 9H), 1.60 (s, 6H), 1.50 (m, 1H).

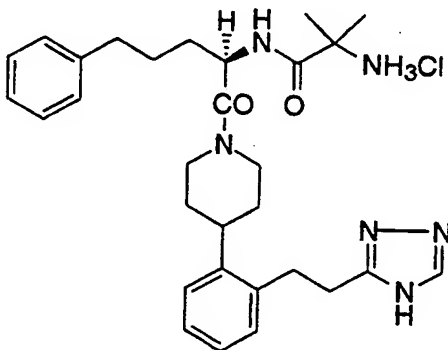
EXAMPLE B39

To a solution of 0.030g of the intermediate prepared in Step C of Example B38 in 2mL of dry acetone was added 13mg of powdered potassium carbonate and 0.006mL of methyl iodide and stirred at RT overnight. The reaction mixture was poured into brine and extracted with CHCl₃. The combined organics were washed with brine, dried over Na₂SO₄, filtered and evaporated to give the alkylated product that was deprotected by the EtOAc/HCl protocol without further purification. This gave 0.006g of the title compound as a mixture of isomers. FAB MS m/e cacl. (for C₃₀H₄₁N₇O₂) 531; found 532.3 (m+1)

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EXAMPLE B40Step A:

This intermediate was prepared in an analogous manner to the BOC material prepared in Step B of Example B38.

Step B:

To a stirred solution of 1.0g of the nitrile from Step A in 10mL of dry ethanol at 0°C was bubbled in HCl(gas) for 1h. The reaction was capped and stored in the freezer overnight. The excess HCl(gas) was removed by bubbling N₂ gas for 1h and ether was added to induce precipitation of the imino-ether intermediate, but only an oily material formed. Hence, the solvents were removed on the rotary

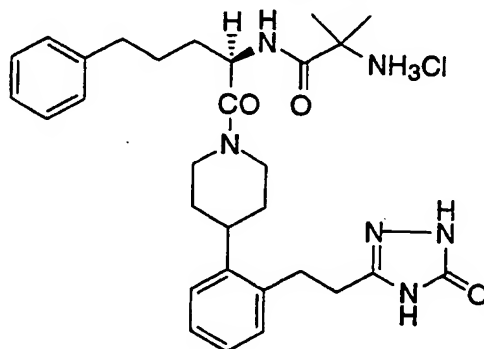
- 193 -

evaporator and the gummy residue was dissolved in CH_2Cl_2 and evaporated twice. Ether was now added and this provided the imino-ether hydrochloride as a foam.

To 0.20g of the above intermediate in 5mL of dichloroethane was added 0.073mL of diisopropylethylamine and 0.030g of formylhydrazine and stirred at room temperature overnight. The reaction mixture was poured into water and extracted with CH_2Cl_2 . The combined organics were washed with brine, dried over Na_2SO_4 and concentrated. The residue thereby obtained was dissolved in 5mL of xylenes and heated at reflux for several hours. The reaction mixture was cooled to room temperature and the xylenes were evaporated. The residue was hydrogenated for 2h in 2mL of methanol and 40mg of 20% palladium hydroxide catalyst. The piperidine thereby obtained was coupled with Intermediate 3 under the standard EDC/HOBT conditions described earlier. The crude product was purified by flash chromatography with CH_2Cl_2 -MeOH- NH_4OH (95:5:1) as the eluent. Removal of the BOC protecting group under the EtOAc/HCl conditions gave the title compound as a white solid.

^1H NMR (400 MHz, CD_3OD mixture of rotamers): 9.15 (s, 1H), 8.16 (bs, 1H), 7.30-7.00 (m, 9H), 4.90 (m, 1H), 4.60 (bs, 1H), 4.10 and 3.95 (2 doublets, 1H), 3.30-3.00 (m, 4H), 3.00-2.60 (m, 5H), 1.90-1.60 (m, 9H), 1.62 (s, 3H), 1.60 (s, 3H), 1.40 (m, 1H).

EXAMPLE B41

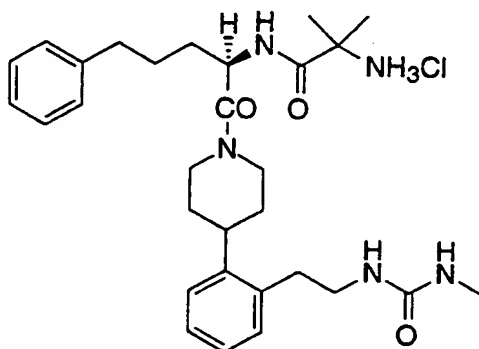


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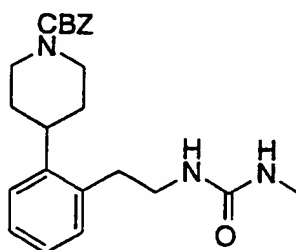
The title compound was prepared in an analogous manner to Example B40 but N-carbomethoxyhydrazine was used in place of N-formylhydrazine.

¹H NMR (400 MHz, CD₃OD mixture of rotamers): 7.30-7.02 (m, 9H), 4.90 (m, 1H), 4.60 (d, 1H), 4.05 and 3.95 (2 doublets, 1H), 3.30-2.95 (m, 5H), 2.80-2.60 (m, 4H), 1.90-1.70 (m, 9H), 1.60 (s, 3H), 1.59 (s, 3H), 1.39 (m, 1H).

EXAMPLE B42



Step A:



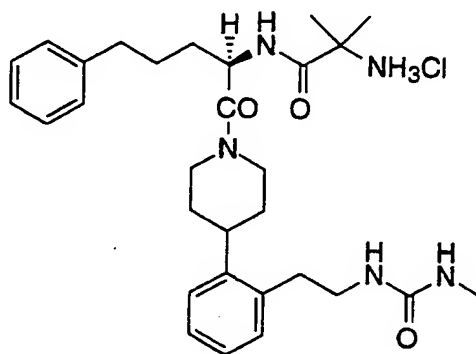
To a solution of 3.0g of the acid intermediate prepared in Step A of Example B37 in 50mL of benzene was added 0.70mL of oxalyl chloride and 3 drops of DMF and stirred at RT for 2h. The benzene was evaporated off and the residue was dissolved in acetone at 0°C. A solution of 1.59g of sodium azide in 5mL of water was added at stirred at 0°C for 1h. The reaction was diluted with ether and water and the organic layer was separated. The organics were washed with brine, dried over Na₂SO₄ and concentrated to give an oily residue. This material was dissolved in dry toluene and heated at reflux for 4h. The reaction mixture

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was concentrated and the isocyanate thereby obtained was stored in the refrigerator.

To 0.40g of the isocyanate in toluene was added 0.80mL of triethylamine and 0.20g of methylamine hydrochloride and stirred for overnight. The reaction mixture was poured into aqueous NaHCO₃ solution and extracted with EtOAc. The combined organics were washed with brine, dried over MgSO₄ and concentrated to give the methylurea that was used without purification.

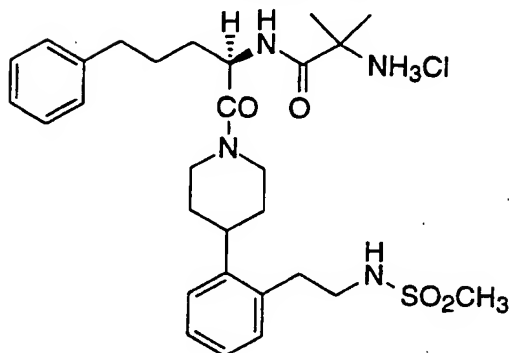
Step B:



The piperidine intermediate prepared in Step A was hydrogenated with Pd(OH)₂ in methanol to remove the CBZ protecting group, coupled with Intermediate 3, purified and deprotected with the EtOAc/HCl protocol as described above to give the title compound.

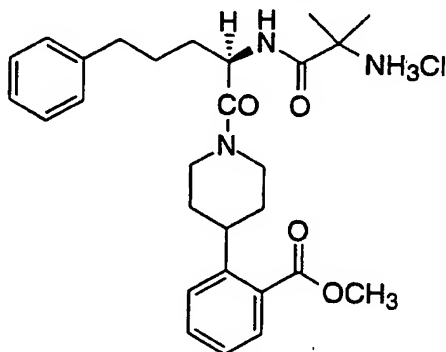
¹H NMR (400 MHz, CD₃OD mixture of rotamers): 8.10 (m, 1H), 7.40-7.00 (m, 9H), 4.95 (m, 1H), 4.63 (d, 1H), 4.10 and 4.00 (2 doublets, 1H), 3.40-3.10 (m, 4H), 2.85-2.90 (m, 2H), 2.70 (s, 3H), 2.80-2.60 (m, 3H), 1.90-1.62 (m, 7H), 1.63 (s, 3H), 1.60 (s, 3H), 1.40(m, 1H).

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EXAMPLE B43

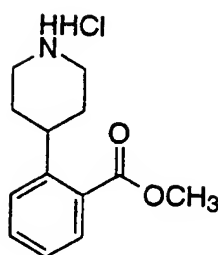
The isocyanate intermediate prepared (0.20g) in Step A of Example B42 was refluxed in 5mL of 6N aqueous HCl overnight. The reaction mixture was washed with ether and the ether layer was discarded. The aqueous layer was basified to pH=10 with aqueous potassium carbonate solution and extracted with CH₂Cl₂. The combined organics were washed with brine, dried over K₂CO₃ and concentrated. This crude amine was converted to the methanesulfonamide by treating it with methanesulfonyl chloride and triethylamine in dichloromethane. After standard work-up the CBZ group was removed by hydrogenation and elaborated to the title compound as discussed previously.

¹H NMR (400 MHz, CD₃OD mixture of rotamers): 7.30-7.00 (m, 9H), 4.85 (m, 1H), 4.55 (d, 1H), 4.00 and 3.90 (2 doublets, 1H), 3.30-3.10 (m, 4H), 2.95-2.83 (m, 2H), 2.80 (2 s, 3H), 2.80-2.60 (m, 3H), 1.90-1.65 (m, 9H), 1.60 (s, 3H), 1.56 (s, 3H), 1.55 (m, 1H).

EXAMPLE B44Step A:

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To a solution of 5.0g of the pyridine aldehyde intermediate prepared in Step A of Example B1 in 100mL of methanol was added 4.0g of sodium cyanide, 5mL of glacial acetic acid and 20g of manganese dioxide and stirred for 2h. The solids were filtered off through a pad of celite and the filtrate was concentrated. The residue was taken up in 100mL of saturated sodium bicarbonate solution and extracted with 3X100mL of ethyl acetate. The combined organics were washed with brine, dried over Na₂SO₄ and concentrated to provide the pyridine methyl ester. This material was dissolved in methanol and 5mL of saturated HCl in ethyl acetate was added and concentrated to give the hydrochloride salt.

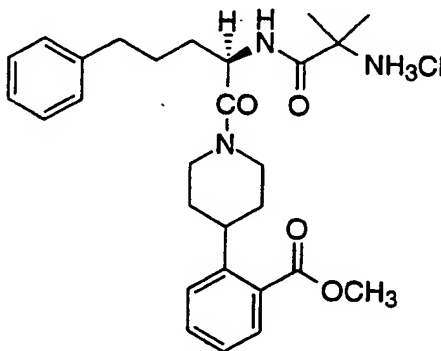
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To 2g of the above pyridine hydrochloride salt in 15mL of methanol was added 0.225g of platinum oxide and hydrogenated at 50psi on the Parr shaker for 2h. The catalyst was filtered off through a pad of celite and washed with methanol. The filtrate was concentrated to give 2.17 of the piperidine hydrochloride as a foam.

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Step B:

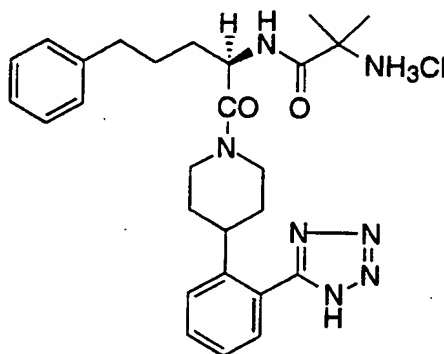
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The title compound was prepared from the compound made in Step A and Intermediate 3 as described previously.

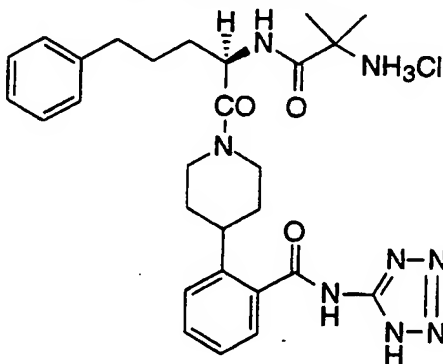
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¹H NMR (400 MHz, CD₃OD mixture of rotamers): 8.10 (t, 1H), 7.78 (dd, 1H), 7.50-7.00 (m, 8H), 4.90 (m, 1H), 4.55 (d, 1H), 3.94 and 3.90 (2 doublets, 1H), 3.85 (s, 3H), 3.80-3.60 (m, 1H), 3.05 (dt, 1H), 2.70-2.50 (m, 4H), 1.90-1.50 (m, 6H), 1.55 (s, 3H), 1.50 9s, 3H), 1.40 (m, 1H).

EXAMPLE B45

The title compound was prepared from the ester intermediate prepared in Step A of Example B44 in an analogous manner to the tetrazole compound prepared in Example B38.

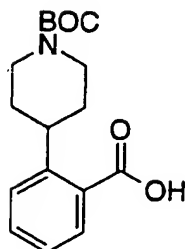
¹H NMR (400 MHz, CD₃OD mixture of rotamers): 7.60-7.45 (m, 2H), 7.45-7.38 (m, 2H), 7.30-7.10 (m, 5H), 4.90 (m, 1H), 3.95 and 3.90 (2 doublets, 1H), 3.30-3.00 (m, 2H), 2.80-2.55 (m, 4H), 1.90-1.63 (m, 7H), 1.65-1.50 (4 singlets, 6H), 1.40 (m, 1H).

EXAMPLE B46

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Step A:

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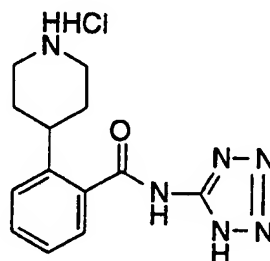


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This compound was prepared in an analogous manner to the protected piperidine acid compound synthesized in Step A of Example B37.

Step B:

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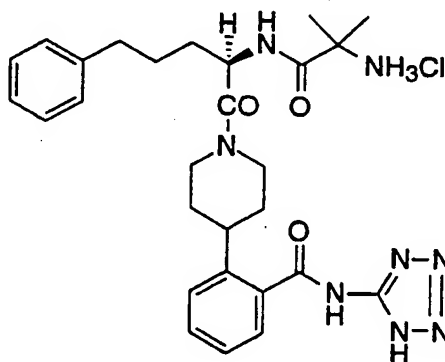


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This intermediate was prepared from the compound synthesized in Step A by using the carbonyldiimidazole method described in Example B35, but amino-tetrazole was used in place of aminopyrazole.

Step C:

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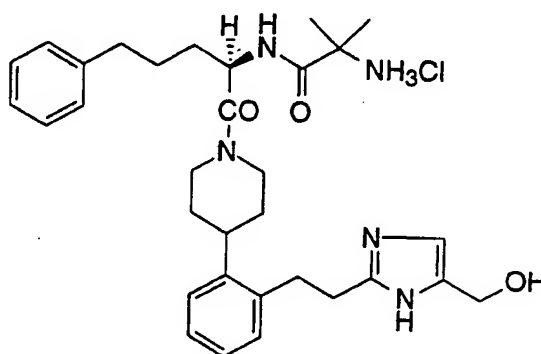
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- 200 -

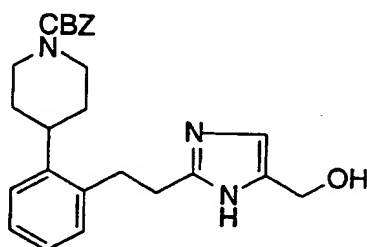
This compound was synthesized from the piperidine intermediate made in Step B and Intermediate 3 by using chemistry presented above.

FAB MS m/e cacl. (for $C_{28}H_{36}N_8O_3$) 532; found 533.1 (m+1)

EXAMPLE B47

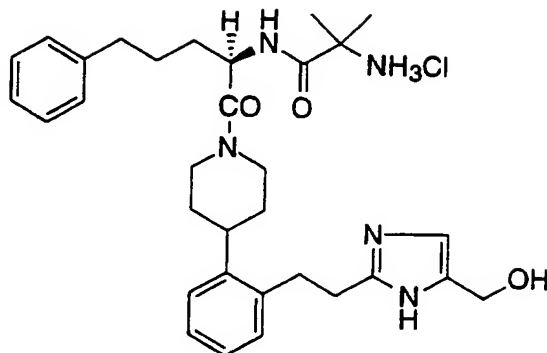


Step A:



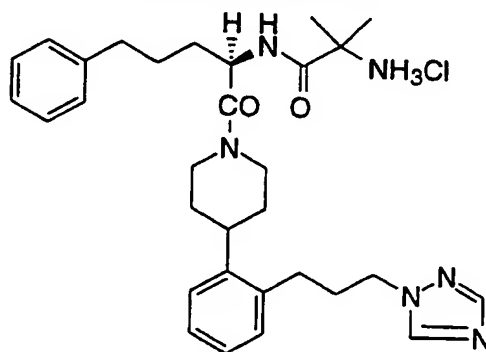
To a solution of 0.30g of the imino-ether intermediate prepared in Step B of Example B40 in 10mL of ethanol was added 0.124g of dihydroxyacetone and heated at 60°C under an ammonia atmosphere in a bomb for 16h. The reaction was cooled to room temperature and the solvent was evaporated. The residue was purified by flash chromatography to give 0.129g of the desired product that was still contaminated with other impurities.

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Step B:

The intermediate prepared in Step A was elaborated to the title compound after removal of the CBZ protecting group, coupling with Intermediate 3, purification, and a final deprotection with the EtOAc/HCl protocol described earlier.

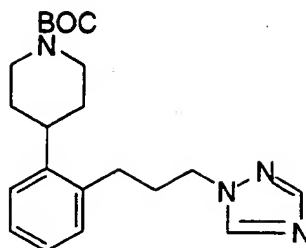
¹H NMR (400 MHz, CD₃OD mixture of rotamers): 8.18 (2 triplets, 1H), 7.30 (s, 1H), 7.30-7.00 (m, 9H), 4.90 (m, 1H), 4.56-4.55 (singlet overlapping a doublet, 3H), 4.05-3.95 (2 doublets, 1H), 3.30-2.95 (m, 4H), 2.95-2.60 (m, 5H), 1.90-1.65 (m, 7H), 1.63 (s, 3H), 1.60 (s, 3H), 1.45 (m, 1H).

EXAMPLE B48

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Step A:

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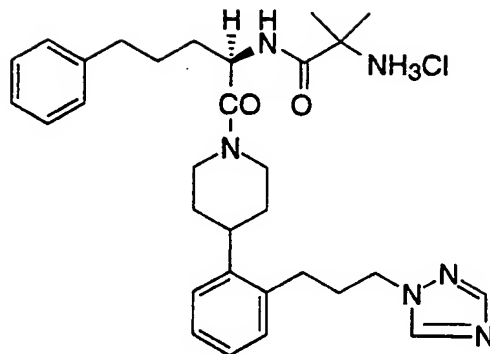
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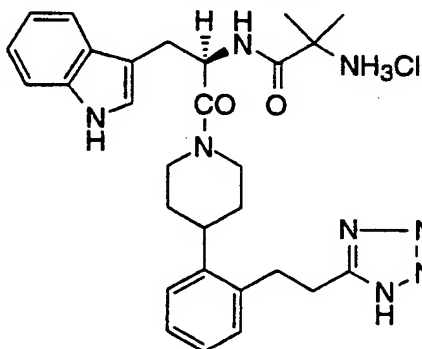
To a solution of 1.0g of the ester prepared in Step B of Example B1 in 50mL of dry THF at 0°C was added 0.20g of lithium aluminum hydride and stirred at room temperature overnight. The reaction was quenched at 0°C with 10mL of water and 10mL of 30% aqueous sodium hydroxide solution. The precipitate was filtered and washed with EtOAc. The ethyl acetate extracts were washed with brine, dried over Na₂SO₄ and concentrated. The crude alcohol was dissolved in 30mL of CH₂Cl₂ and 1.3mL of triethylamine and 1.4g of di-*t*-butylcarbonate was added at 0°C and then stirred at RT for 2h. The reaction was poured into saturated NaHCO₃ solution and extracted with CH₂Cl₂. The combined organics were washed with 0.50N HCl, brine, dried over Na₂SO₄ and concentrated. This material was purified by flash chromatography with hexane-acetone (5:1) as the eluent.

The alcohol obtained above was dissolved in 10mL of CH₂Cl₂ at 0°C and 0.45mL of triethylamine and 0.14mL of methanesulfonyl chloride were added and stirred for 1h. The reaction was diluted with water and extracted with CH₂Cl₂. The combined organics were washed with 0.50N HCl, brine, dried over Na₂SO₄ and concentrated. The crude mesylate was heated at 60°C with 0.20g of the sodium salt of 1,2,4-triazole in 10mL of dry DMF for 3h. The reaction was cooled to RT and quenched with aqueous ammonium chloride solution. The reaction mixture was extracted with ether (3X15mL). The combined organics were washed with brine, dried over Na₂SO₄, filtered and concentrated. This gave the triazole product that was used without purification.

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Step B:

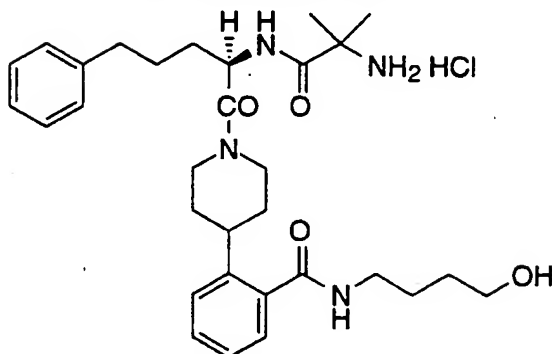
The BOC protecting from the piperidine synthesized in Step A was removed with the TFA procedure as described previously and elaborated to the title compound by coupling with Intermediate 3, purification and a final deprotection with the EtOAc/HCl protocol. FAB MS m/e cacl. (for C₃₁H₄₂N₆O₂) 530; found 531.4 (m+1)

EXAMPLE B50

Prepared as described in Example B40 Step B but Intermediate 1 was used in place of Intermediate 3.

¹H NMR (400 MHz, CD₃OD mixture of rotamers): 8.32 and 8.20 (2 doublets, 1H), 7.65 and 7.58 (2 doublets, 1H), 7.40 and 7.35 (2 doublets, 1H), 7.25-7.00 (m, 6H), 6.50 (d, 1H), 5.30-5.20 (m, 1H), 4.58 and 4.55 (2 doublets, 1H), 4.10 and 3.95 (2 doublets, 1/2H), 3.90 (d, 1/2H), 3.40-3.00 (m, 7H), 2.70-2.45 (m, 3H), 2.80-2.50 (m, 2H), 1.60 (s, 6H), 1.34 (d, 1H), 0.95 (d, 1/2H), 0.70 (dt, 1/2H).

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EXAMPLE B50 A

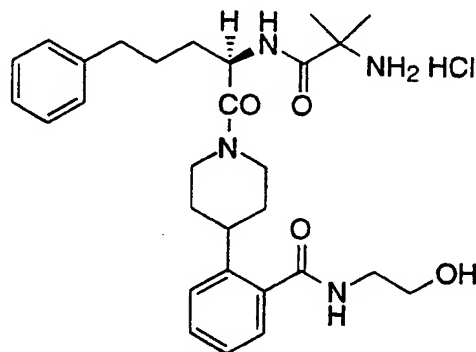
To a solution of 0.330g of the acid intermediate prepared in Step A of Example B15 in 3.3mL of dry THF was added 0.196g of carbonyldiimidazole and heated to 60°C for 2h. A small aliquot of the reaction mixture was removed and to the remaining solution was added 0.10mL of 4-aminobutanol and heated for 2h. The reaction mixture was concentrated, taken up in chloroform, washed twice with water, once with 1M K₂HPO₄, brine, dried over MgSO₄, filtered and concentrated to provide a residue that was separated by prep TLC (1mm plate) with CHCl₃-MeOH-NH₄OH (90:10:1) as the eluent to give the desired intermediate.

To a solution of 0.20g of the above material in 2mL of anisole was added 3-4mL of TFA and allowed to stand at rt for 30 min. The volatiles were removed under reduced pressure and the residue was partitioned between chloroform and 1M K₂HPO₄ and basified to pH>9 with NaOH. The organic phase was separated and the aqueous phase was extracted with chloroform. The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated to provide a gum that was separated by prep TLC (1mm plate) with CHCl₃-MeOH-NH₄OH (90:10:1) as the eluent to give the desired product.

¹H NMR (200MHz; CDCl₃ mixture of rotamers): 8.24 (d, J=8); 7.42-7.07 (m); 6.16 ("dd", J=12, 4); 4.97-4.8 (m); 4.69 (bd, J=13); 3.93 ("bt", J~10); 3.75-3.64 (m); 3.54-3.4 (m); 3.35-3.16 (m); 3.07 (quart., J=13); 2.77-2.5 (m); 1.97-1.42 (m); 1.34 (s). FAB MS Calc. for C₃₁H₄₄N₄O₄: MW=536.34; found m/e = (m+1) 537.1.

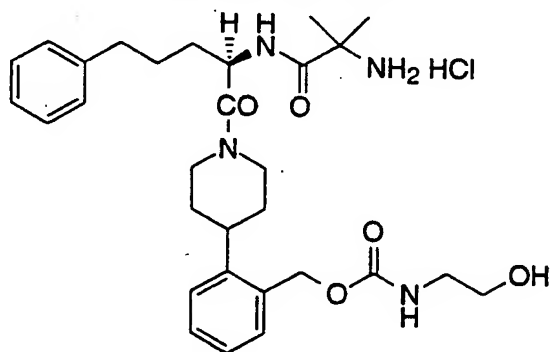
- 205 -

A solution of 0.150g of the above free base was lyophilized from 0.50mL of acetic acid and 0.030mL of conc. HCl to give title compound.

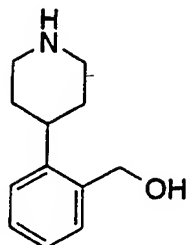
EXAMPLE B50B

Prepared in an analogous manner to the compound prepared in Example B50A but ethanolamine was used in place of 4-aminobutanol. ¹H NMR (200MHz; CDCl₃ mixture of rotamers) : 8.22 (d, J=8); 7.45-7.05 (m); 6.58 (dt, J=16, 5); 4.88 (bs); 4.64 (bd, J=12); 3.90 (t, J=11); 3.79 (bs); 3.65-3.50 (m); 3.25-3.15 (m); 3.05 (quart., J=12); 2.8-2.5 (m); 2.32 (vbs); 2.0-1.77 (m); 1.77-1.45 (m); 1.35 (s). FAB MS Calc. for C₂₉H₄₀N₄O₄ : MW=508.30; found m/e = (m+1) 509.2.

A solution of 0.029g of the above free base was lyophilized from 0.50mL of acetic acid and 0.010mL of conc. HCl to give title compound.

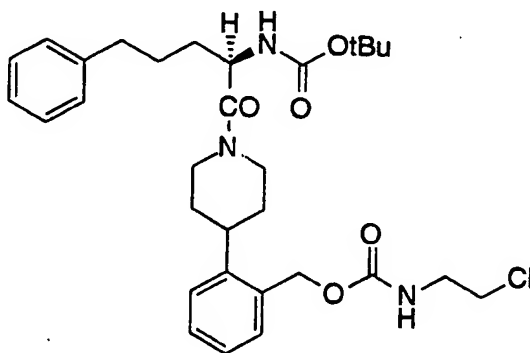
EXAMPLE B50C

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Step A:

To a solution of 0.379g of the free base (prepared by basification to pH>9 with NaOH and extraction with CHCl₃) of the intermediate prepared in Step A of Example B44 in 20mL of dry THF was added 5.5mL of 1M solution of lithium aluminum hydride in THF and stirred overnight. The reaction was quenched with 10mL of 30% aqueous NaOH, the organic phase was decanted, and the paste was extracted with ethyl acetate. The combined organics were dried over MgSO₄ and concentrated. Purification of the residue by prep TLC (1mm plate) gave the desired amino alcohol.

¹H NMR (200MHz; CDCl₃ mixture of rotamers) : 7.38-7.13 (m); 4.75 (s); 3.22 (bd, J=12 Hz); 3.1-2.92 (m); 2.81 (td, J=10, 4 Hz); 2.13 (bs); 1.85-1.6 (m).

Step B:

The intermediate prepared in Step A was coupled with (2R)-N-t-BOC-5-phenyl pentanoic acid under the standard EDC/HOBT protocol as described above and purified by prep TLC (1mm plate).

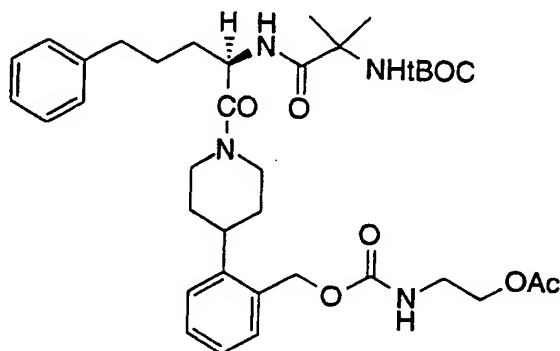
To a solution of 0.145g of the above coupled product in 2mL of CDCl₃ was added 0.50mL of 2-chloroethylisocyanate and was heated

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at 60°C for 6h and allowed to stand at RT overnight. Prep TLC of this mixture with hexane-EtOAc (1:1) as the eluent gave 0.11g of the desired carbamate.

¹H NMR (200MHz; CDCl₃ mixture of rotamers) : 7.45-7.05 (m); 5.50 (bd, J=6); 5.19 (s); 5.14 (bs); 4.86-4.45 (bdd?); 4.11 (bd, J=7); 3.93 (bt, J=12); 3.72-3.42 (bm); 3.2-2.88 (m); 2.8-2.5 (bm); 1.95-1.55 (m); 1.44 (s).

Step C:



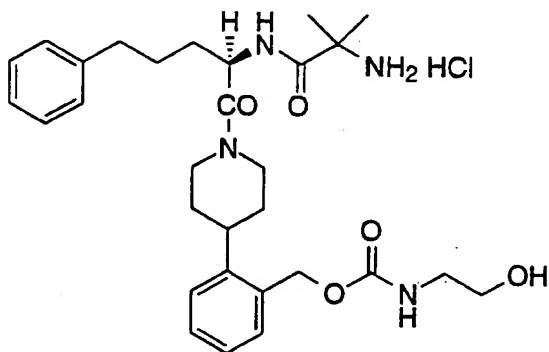
The intermediate prepared in Step B was deprotected with EtOAc/HCl and the hydrochloride salt thereby obtained was coupled with N-t-BOC- α -methylalanine under standard EDC/HOBT conditions. This material was purified by prep TLC (1mm plate) with hexane-EtOAc (1:1) as the eluent. ¹H NMR (200MHz; CDCl₃ mixture of rotamers) : 7.40-7.04 (m); 5.19 (s); 5.17 (bs); 4.98 (s); 4.92 (bs); 4.72 (bd, J=13); 4.54 (bd, J=13); 4.18-4.04 (m); 3.95 (bt, J=13); 3.68-3.45 (m); 3.2-2.85 (m); 2.78-2.47 (m); 2.0-1.6 (m); 1.6-1.4 (m); 1.44 (s).

Approximately 85 mg (0.13 mmoles) of the above product was taken up in 1.0 mL of DMSO-d₆ to which was added 38 mg (0.37 mmoles) of LiOAc·2H₂O, and 30 mg (0.2 moles) of NaI; the solution was heated in an 80°C oil bath over night. The reaction mixture was then taken to a gum under a nitrogen stream. It was then partitioned in a mixture of CHCl₃ and water, the organic phase separated, dried with anhydrous MgSO₄, filtered, and after concentration to a gum under reduced pressure, purified by preparative tlc on one 8"x 8" x 1,000m plate in 1:1 EtOAc: hexane to give 85 mg of the title compound.

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¹H NMR (200MHz; CDCl₃ mixture of rotamers) : 7.40-7.04 (m); 5.19 (s); 5.17 (bs); 4.98 (s); 4.92 (bs); 4.72 (bd, J=13); 4.54 (bd, J=13); 4.18-4.04 (m); 3.95 (bt, J=13); 3.68-3.45 (m); 3.2-2.85 (m); 2.78-2.47 (m); 2.0-1.6 (m); 1.6-1.4 (m); 1.44 (s). : 7.4-7.0 (m); 7.88-7.69 (bm); 5.4 (s); 5.14 (s); 4.95-4.74 (m); 4.67 (bd, J=12); 4.38 (bd, J=13); 4.15-4.02 (m); 3.93 (bt, J=14); 3.50-3.30 (m); 3.18-2.8 (m); 2.75-2.35 (bm); 2.01 (s); 1.9-1.7 (bm); 1.5-1.3 (m); 1.40 (s).

Step D:

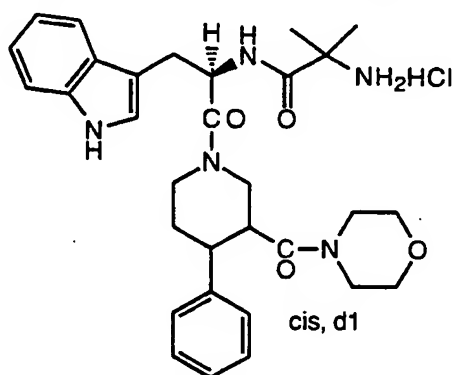


To 49 mg of the intermediate from Step D in 0.5 mL of methanol was added 1-2mL of conc. H₂SO₄. After standing over night a 1M solution of K₂HPO₄ was added and the reaction mixture was taken to dryness under a stream of nitrogen and the residue was partitioned between CHCl₃ and 1M K₂HPO₄, adjusted to pH >9 with NaOH. The organic phase was removed and the aqueous phase extracted several more times with CHCl₃. The combined organic phases were dried with anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resultant gum was subjected to preparative tlc on one 8" x 8" x 1,000m silica gel GF plate using 1:10:90 (conc. NH₄OH:MeOH:CHCl₃); two major bands were observed. Isolation of the faster band afforded the title compound. ¹H NMR (200MHz; CDCl₃ mixture of rotamers) : 7.4-7.05 (m); 5.44-5.12 (m); 5.18 (s); 5.12-4.8 (m); 5.05 (s); 4.69 (bd, J=12); 4.52 (bd, J=12); 4.12 (bs); 3.93 (bt, J=12); 3.78-3.63 (m); 3.44-3.24 (bm); 3.24-2.83 (m); 2.83-2.5 (m); 2.01-1.6 (m); 1.6-1.35 (m); 1.45 (s). FAB MS Calc. for C₃₅H₅₀N₄O₇ ; MW= 638.37; found m/e = (m+1) 639.3.

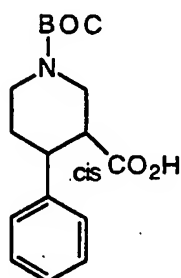
- 209 -

A solution of 23 mg (0.042 mmoles) of the above free base in 0.5 mL of acetic acid in a vial was treated with 0.005 mL (0.06 mmoles) of conc. HCl, shell frozen, and lyophyllized overnight to give the title compound.

EXAMPLE B51 (cis, d₁)



Step A:

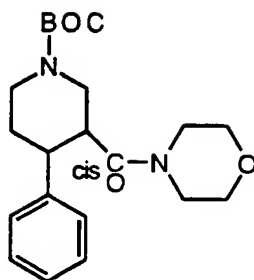


To a solution of 4.1g of the intermediate prepared in Example B12 Step A-1 in 25 ml of ethanol was added 25 ml of 6 N NaOH and stirred 12 hours. The mixture was diluted with water and extracted with ether. The organic layer was discarded. The aqueous layer was cooled to 0°C and acidified with conc. HCl and then extracted with ether. The organic layer was dried over sodium sulfate, filtered and concentrated to give 2.57g of the crude acid. The crude acid (438 mg) was dissolved in methanol and hydrogenated over Pd(OH)₂ at one atmosphere for 16 hours. The mixture was filtered through Celite and the filtrate was concentrated under vacuum to give the desired compound (370 mg).

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Step B:

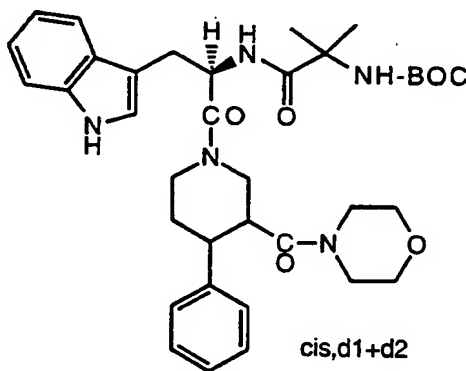
5



To the intermediate prepared in Step A (100 mg) in
10 chloroform was added morpholine (0.35 ml), EDC (95 mg), and HOBt
(49 mg). The reaction was stirred for 12 hours at room temperature and
was diluted with methylene chloride and then washed with water and
brine. The organic layer was dried over sodium sulfate, filtered and
concentrated. The residue was purified by prep TLC (hexanes/ethyl
15 acetate=1/1) to give the desired product (71 mg).

Step C:

20



25

To the intermediate prepared in Step B (71 mg) in ethyl
acetate was bubbled in HCl(g) at 0°C for 15 seconds. The mixture was
allowed to stand at room temperature for 30min., concentrated to give a
solid (64 mg). To this crude material (32 mg) in 2 ml of chloroform was
30 added Intermediate 1 (43 mg), EDC (29 mg), HOBt (15 mg) and
triethylamine (21 mL). The reaction was stirred at room temperature for
3 hours and poured into water and extracted with methylene chloride,
dried over sodium sulfate and concentrated. Purification (prep TLC,

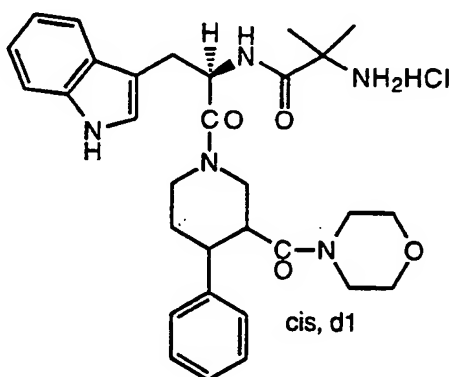
- 211 -

methylene chloride/methanol=20/1) gave two diastereomers (d₁, the less polar diastereomer, 14 mg; d₂, the more polar diastereomer, 16 mg).

Step D:

5

10

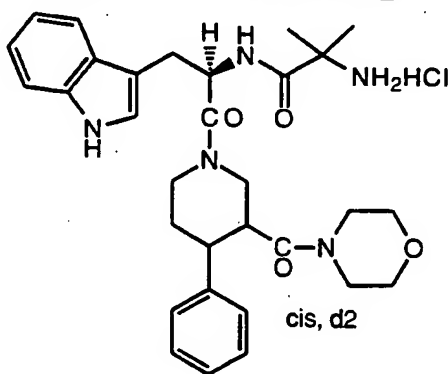


The less polar diastereomer (d₁, 14 mg) prepared in Step C was dissolved in ethyl acetate and treated with HCl(g) at 0°C for 15 seconds. After 30 minutes at room temperature the mixture was concentrated to give the desired product (10 mg).
FAB-MS: 546.3 (M+1)

20

EXAMPLE B52 (cis, d₂)

25

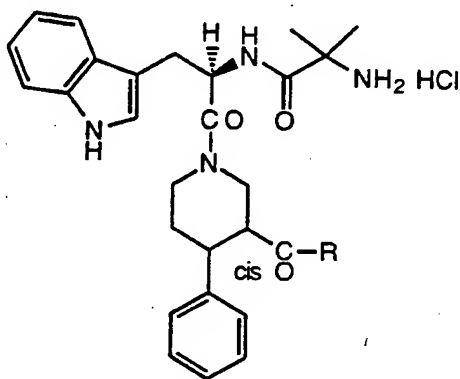


30

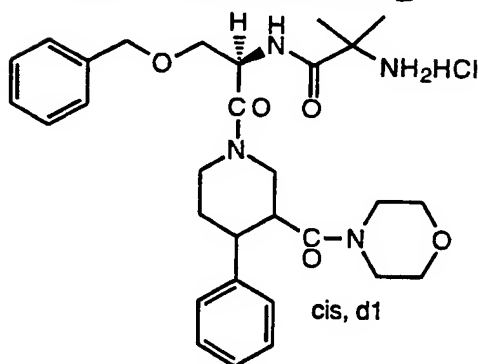
The title compound (12 mg) was prepared from the more polar diastereomer (d₂, 16 mg) obtained in Example B51, Step C by the procedure described in Example B51, Step D.
FAB-MS: 546.3 (M+1)

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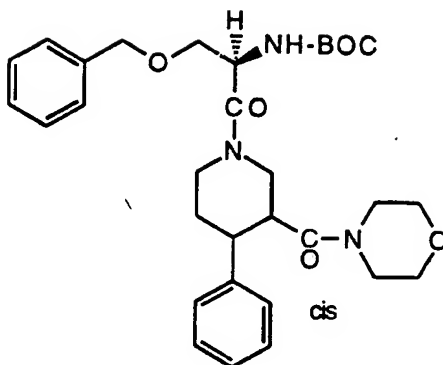
The compounds 1-7 shown in Table B3 were prepared according to the procedures reported above (using different amines in the coupling step). Details are available in Example B51 Steps B, C and D.

TABLE B3

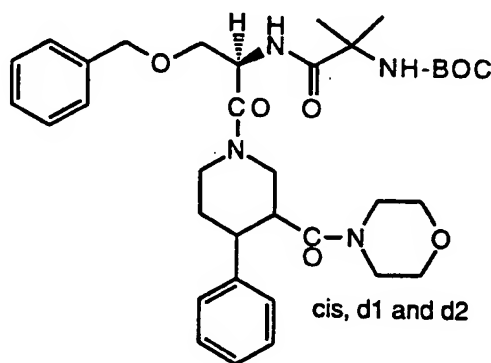
| | | R | FAB-MS (M+1) |
|---|--------------------------------|---------------------|--------------|
| 1 | d ₁ +d ₂ | thiomorpholine | 562.2 |
| 2 | d ₁ +d ₂ | pyrrolidine | 530.2 |
| 3 | d ₁ +d ₂ | N-methylpiperazine | 559.3 |
| 4 | d ₁ +d ₂ | piperidine | 544.3 |
| 5 | d ₁ +d ₂ | ethanolamine | 520.2 |
| 6 | d ₁ +d ₂ | dimethylamine | 504.3 |
| 7 | d ₁ +d ₂ | glycine ethyl ester | 562.3 |

EXAMPLE B53 (cis, d₁)

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Step A:

The intermediate prepared from Example B51, Step B in ethyl acetate was treated with HCl(g) at 0°C for 15 seconds and allowed to stand at room temperature for 30 min. The mixture was concentrated to dryness to give the crude material. To this crude material (99 mg) in 3 ml of chloroform was added N-t-BOC-O-benzyl-D-serine (107 mg), EDC (92 mg), HOBt (47 mg) and triethylamine (67 ml) and stirred at room temperature for 3 hours and poured into water. The mixture was extracted with methylene chloride and dried over sodium sulfate, and concentrated. Purification of the residue by RPLC (chromatatron, methylene chloride/methanol=20/1) gave the desired product (97 mg).

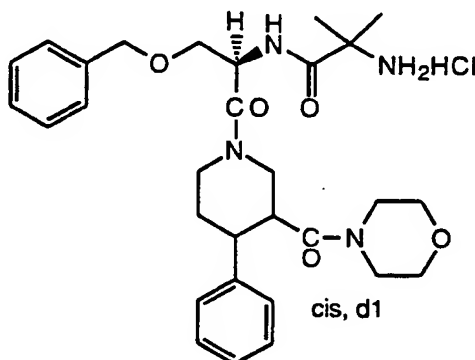
Step B:

The intermediate prepared from Step B (97 mg) in ethyl acetate was treated with HCl(g) at 0°C for 15 seconds and allowed to stand at room temperature for 30 minutes. The reaction mixture was concentrated to give a residue that was dissolved in 2 ml of chloroform

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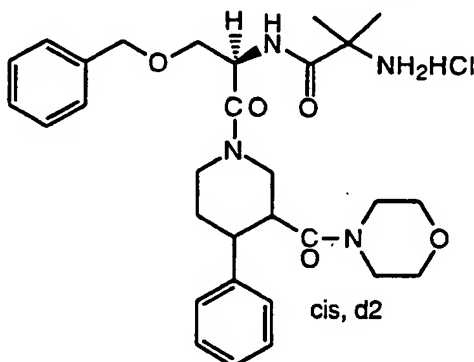
and reacted with N-t-BOC- α -methylalanine (52 mg) in the presence of EDC (62 mg), HOBt (36 mg) and triethylamine (40 ml). After 64 hours at room temperature the reaction mixture was poured into water and extracted with methylene chloride. The combined extracts were dried
5 over sodium sulfate, filtered and concentrated to give a residue that was purified by RPLC (chromatatron, methylene chloride/methanol=20/1) to give two diastereomers (d₁, the less polar diastereomer, 65 mg; d₂, the more polar diastereomer, 23 mg).

10 Step C:



20 The less polar diastereomer (d₁, 65 mg) prepared from Step B in ethyl acetate was treated with HCl(g) at 0°C for 15 seconds. After standing at room temperature for 30 minutes, the mixture was concentrated to give the desired product (58 mg).
FAB-MS: 537.4 (M+1)

25 EXAMPLE B54 (cis, d₂)



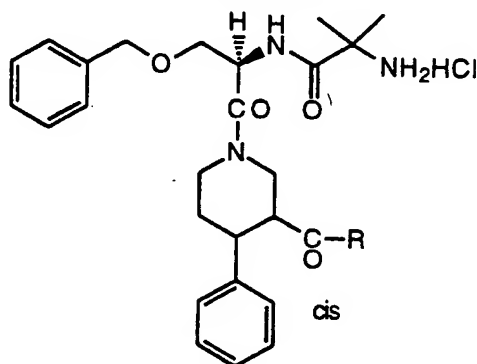
- 215 -

The title compound (20 mg) was prepared from the more polar diastereomer (d₂, 23 mg) obtained in Example B53, Step C by the procedure described in Example B51, Step D.

FAB-MS: 537.3 (M+1).

The compounds 1-6 shown in Table B4 were prepared as described above (with different amines). The details of the syntheses are available in Example B51, Step B and Example B53, Steps A, B and C.

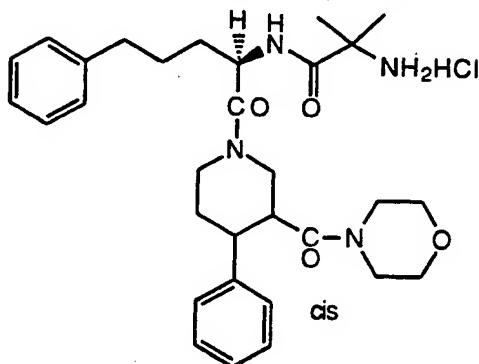
TABLE B4



| | | | R | FAB-MS (M+1) |
|----|---|--------------------------------|--------------------|--------------|
| 20 | 1 | d ₁ +d ₂ | thiomorpholine | 553.3 |
| | 2 | d ₁ +d ₂ | pyrrolidine | 521.3 |
| | 3 | d ₁ | N-methylpiperazine | 550.4 |
| | 4 | d ₂ | N-methylpiperazine | 550.4 |
| 25 | 5 | d ₁ +d ₂ | piperidine | 535.4 |
| | 6 | d ₁ +d ₂ | dimethylamine | 495.2 |

30

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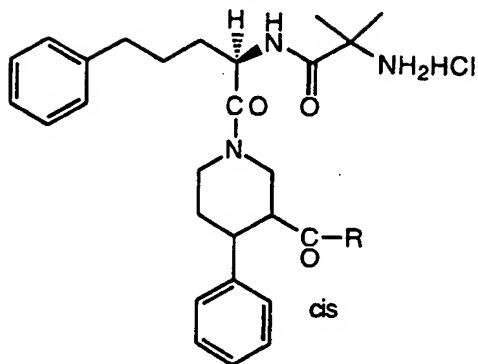
EXAMPLE B55 (cis, d₁+d₂)

The intermediate prepared from Example B51, Step B in ethyl acetate was treated with HCl(g) at 0°C for 15 seconds. The reaction mixture was allowed to stand at room temperature for 30 minutes and concentrated to give the crude product. To this material (209 mg) in 10 ml of chloroform was added Intermediate 3 (295 mg), EDC (202 mg), HOBt (105 mg) and triethylamine (147 ml) and stirred at room temperature for 16 hours and poured into water. The mixture was extracted with methylene chloride and dried over sodium sulfate, concentrated and the residue was purified by RPLC (chromatatron, methylene chloride/methanol=20/1) to give the desired product (387 mg). This mixture of diastereomers in ethyl acetate was treated with HCl(g) at 0°C for 15 seconds and allowed to stand at room temperature for 30 minutes. The reaction mixture was concentrated to give the desired product (330 mg).

FAB-MS: 535.3

The compounds shown in Table B5 were prepared according to established procedures (with ethanolamine instead of morpholine) as exemplified in Example B51, Step B and Example B53, Steps A, B and C using Intermediate 3.

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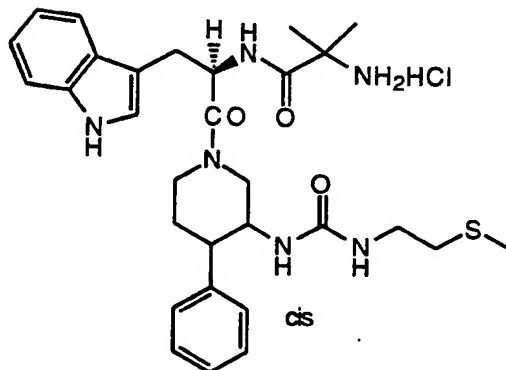
TABLE B5

5

10

| | R | FAB-MS (M+1) |
|---|----------------|--------------|
| 1 | d ₁ | ethanolamine |
| 2 | d ₂ | ethanolamine |

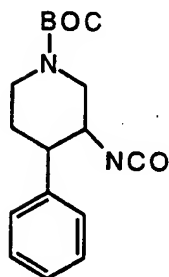
15

EXAMPLE B56 (cis, d₁+d₂)

20

Step A:

25

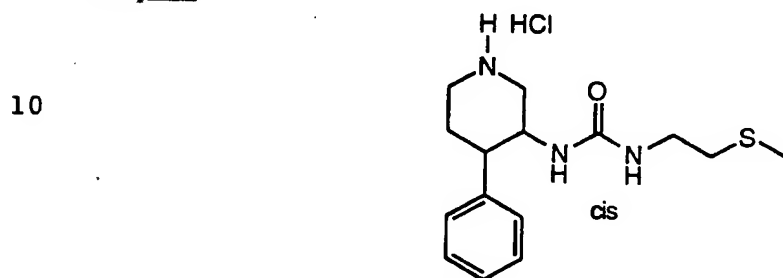


30

To the intermediate prepared in Example B51, Step A (1.15 g) in benzene (80 ml) was added oxalyl chloride (365 ml) and DMF (2 drops) at 0°C and stirred at 0°C for 10 minutes and room temperature for 2 hours and concentrated to give the acyl chloride. To a solution of acyl

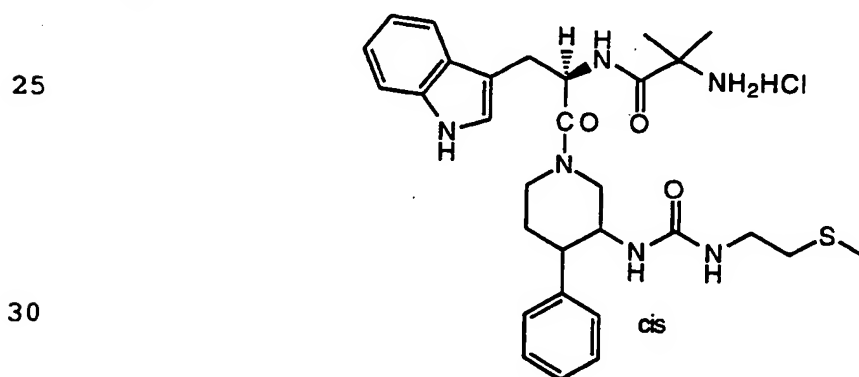
- 218 -

chloride at 0°C in acetone (10 ml) was added sodium azide (741 mg) in water (3 ml) and stirred at room temperature for 45 minutes. The mixture was extracted with ether, washed with water, brine, dried over MgSO₄, filtered and evaporated to give the acyl azide which was dissolved in toluene (35 ml) and was refluxed 12 hours to give the isocyanate (1.02 g).

Step B:

15 A solution of the intermediate prepared in Step A (55 mg) and 2-(methylthio)ethylamine (147 mg) in toluene (5 ml) was refluxed for one hour. The reaction was quenched with 1N HCl and extracted with ether and then dried over sodium sulfate. Concentration and purification (chromatatron, methylene chloride/methanol=20/1) gave the desired urea. Deprotection of the BOC protecting group under conditions described above gave the desired product (40 mg).

20

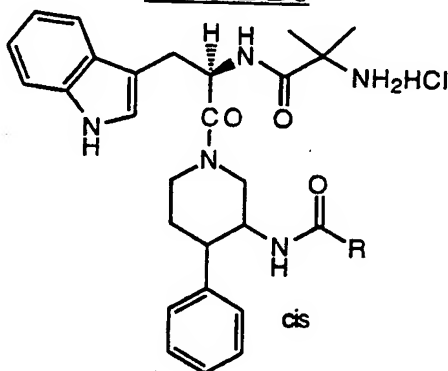
Step C:

To the intermediate prepared in Step B (20 mg) in 2 ml of chloroform was added Intermediate 1 (28 mg), EDC (19 mg), HOBT (10 mg) and triethylamine (14 ml). The reaction was stirred at room

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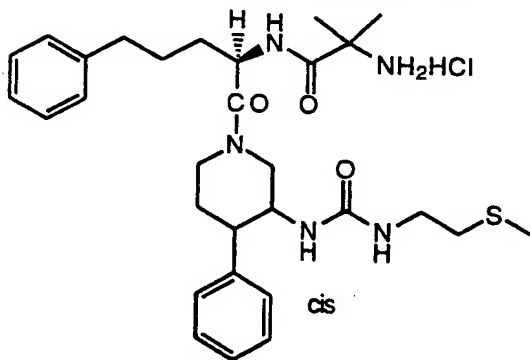
temperature for 16 hours and poured into water. The mixture was extracted with methylene chloride and dried over sodium sulfate. Concentration and purification (chromatatron, methylene chloride/methanol=20/1) gave desired product. The mixture was treated with HCl in EtOAc to give the final product (6 mg). FAB-MS: 565.3 (M+1)

The compounds shown in Table B6 were prepared according to established procedures (with different amines or alcohol).

TABLE B6

| | | | |
|----|---|-----------------------|---------------|
| | | R | FAB-MS (M+1). |
| | 1 | d1+d2 ethanol | 520.3 |
| | 2 | d1+d2 morpholine | 561.4 |
| | 3 | d1+d2 ethanolamine | 535.3 |
| 25 | 4 | d1+d2 ethylamine | 519.2 |

EXAMPLE B57 (cis, d1+d2)

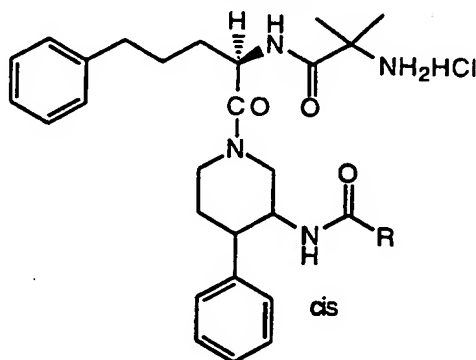


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To a solution of the intermediate prepared from Example B56, Step B (20 mg) in 1 ml of chloroform was added Intermediate 3 (28 mg), EDC (19 mg), HOBt (10 mg) and triethylamine (14 ml). The reaction was stirred at room temperature for 16 hours and poured into water. The mixture was extracted with methylene chloride and dried over sodium sulfate. Concentration and purification (chromatatron, methylene chloride/methanol=20/1) gave the desired product Deprotection of this diastereomeric mixture with HCl/EtOAc gave the final product (8 mg). FAB-MS: 554.4 (M+1)

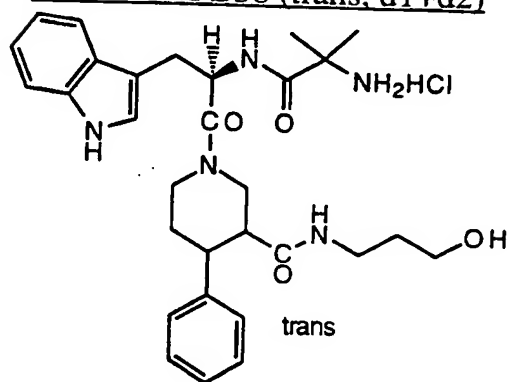
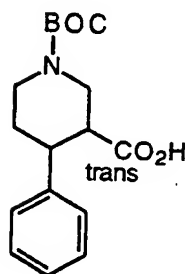
The compounds shown in Table B7 were prepared according to the above-described procedures (with ethanol and different amines).

TABLE B7

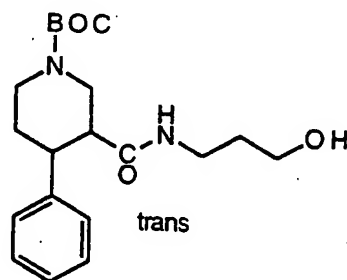


| | | R | FAB-MS (M+1) |
|---|-------|----------------|--------------|
| 1 | d1+d2 | ethanol | 509.3 |
| 2 | d1+d2 | morpholine | 550.4 |
| 3 | d1+d2 | ethanolamine | 524.3 |
| 4 | d1+d2 | thiomorpholine | 566.2 |

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EXAMPLE B58 (trans, d1+d2)Step A:

To a solution of the intermediate prepared from Example B14, Step A (2.52 g) in ethanol was added 6N NaOH. The mixture was refluxed for 3 hours and then concentrated. The residue was diluted with water and acidified with 0.5 N hydrochloric acid and extracted with ether. The organic layer was dried over sodium sulfate, filtered and concentrated to give the desired product (2.12 g).

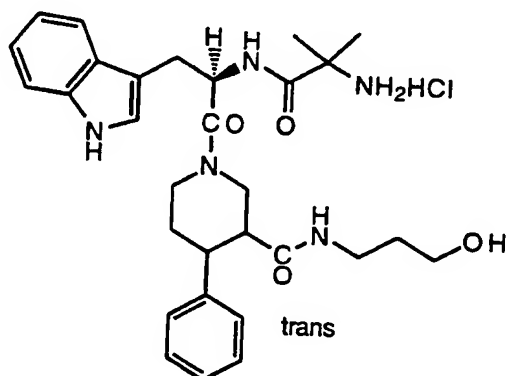
Step B:

To a solution of the intermediate prepared from Step A (15 mg) in 1 ml of chloroform was added 4-amino-1-butanol (9 ml), EDC (19 mg), and HOBt (7.5 mg). The reaction was stirred at room temperature

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for 2 hours and poured into water. The mixture was extracted with methylene chloride and dried over sodium sulfate. Concentration and purification (chromatatron, methylene chloride:methanol=20/1) gave the desired product.

Step C:



The intermediate prepared from Step B was deprotected with the HCl/EtOAc protocol. To this crude material in 1 ml of chloroform was added Intermediate 1 (18 mg), EDC (19 mg), HOBt (7.5 mg) and triethylamine (20 ml). The reaction was stirred at room temperature for 4 hours and poured into water. The mixture was extracted with methylene chloride and dried over sodium sulfate. Concentration and purification (PLC, methylene chloride/methanol=10/1) gave the desired product (20 mg, unseparable diastereomer mixture) that was treated with HCl (gas) in EtOAc to give the desired product (18 mg).

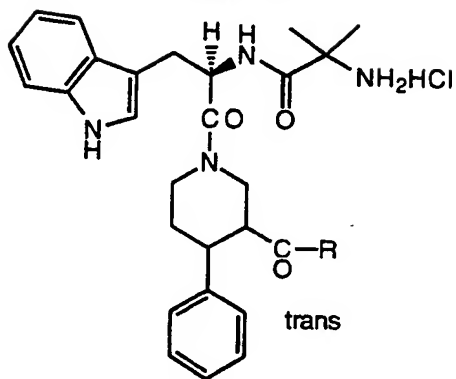
¹H NMR (400 MHz, CD₃OD, mixture of diastereomers and rotamers): 7.73 (d, 8 Hz, 1/2 H), 7.65 (d, 8 Hz, 1/2 H), 7.54-6.98 (m, 7 1/2 H), 6.87 (t, 7 Hz, 1 1/2 H), 5.25 (m, 1 H), 4.53 (m, 1 H), 3.89 (m, 1 H), 3.39-2.47 (m, 10 H), 1.71-0.93 (m, 5 H), 1.61 (s, 3/2H), 1.60 (s, 3 H), 1.58 (s, 3/2 H), 0.41 (m, 1/2 H), 0.11 (m, 1/2 H).

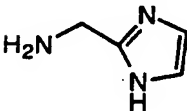
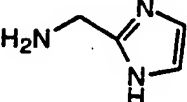
FAB-MS: 548.2 (M+1).

The compounds shown in Table B8 were prepared according to the above procedures (with different amines).

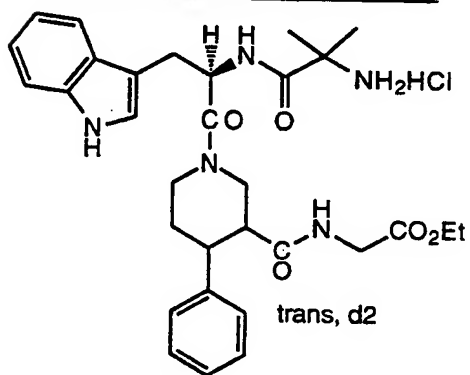
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TABLE B8



| | | R | FAB-MS (M+1) |
|----|---|---|--------------|
| | 1 | d1+d2 | |
| | 2 | d1+d2 | 504.3 |
| | 3 | d1+d2 | 546.3 |
| 15 | 4 | d1 | 520.2 |
| | |  | 556.1 |
| | 5 | d2 | 556.1 |
| 20 | |  | |

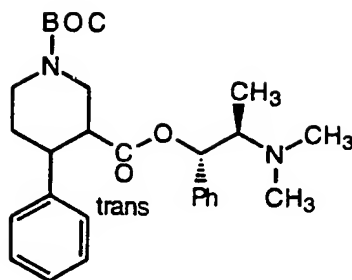
EXAMPLE B59 (trans. d2)



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Step A:

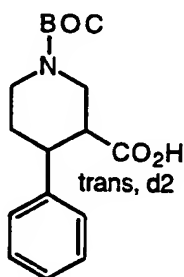
5



To a solution of the intermediate prepared from Example
10 B58, Step A (915 mg) in chloroform was added (1R, 2R)-N-methyl
pseudoephedrine (590 ml), EDC (1.14 g), and a catalytic amount of
DMAP. The reaction was stirred at room temperature for 12 hours and
poured into water. The mixture was extracted with methylene chloride
and dried over sodium sulfate. Concentration and purification (MPLC,
15 hexanes/ethyl acetate=3/1) gave two diastereomers (d1, the less polar
diastereomer, 316 mg; d2, the more polar diastereomer, 138 mg).

Step B:

20



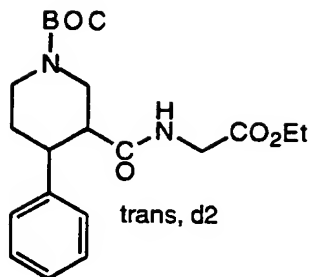
25

A solution of the more polar intermediate prepared in Step A
(138 mg) in methanol was hydrogenated with Pd(OH)₂/C at one
atmosphere for a couple of hours. The mixture was filtered through
Celite and the filtrate was concentrated. The residue was redissolved in
ether and washed with 1N hydrochloric acid. The aqueous layer was
30 discarded. The organic layer was dried over sodium sulfate, filtrated and
concentrated to give the desired product (84 mg).

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Step C:

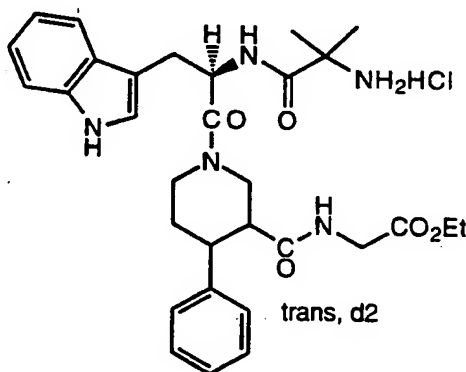
5



To the intermediate prepared from Step B (16 mg) in
10 chloroform was added glycine ethyl ester hydrochloride salt (21 mg),
EDC (19 mg), HOBt (13 mg) and triethylamine (35 ml). After 3 hours at
room temperature the mixture was diluted with methylene chloride and
then washed with water and brine. The organic layer was dried over
15 sodium sulfate, filtered and concentrated. The residue was purified by
prep TLC (hexanes/ethyl acetate=1/1) to give the desired product (16
mg).

Step D:

20



25

The intermediate prepared in Step C (8 mg) was treated with
HCl(gas) in EtOAc to give a crude hydrochloride. To this crude material
30 in 1 ml of chloroform was added intermediate 1 (8 mg), EDC (8 mg),
HOBt (5 mg) and triethylamine (8 ml). The reaction was stirred at room
temperature for 12 hours and poured into water. The mixture was
extracted with methylene chloride and dried over sodium sulfate.
Concentration and purification (PLC, hexanes/ethyl acetate=1/2) gave the

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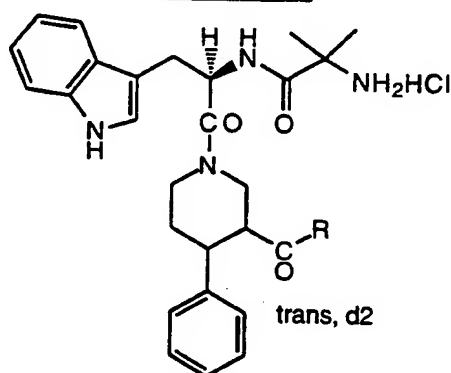
desired product which was deblocked with the HCl/EtOAc protocol to give the desired product (11 mg).

¹H NMR (400 MHz, CD₃OD, mixture of rotamers): 7.73 (d, 8 Hz, 1/2 H), 7.54 (d, 8 Hz, 1/2 H), 7.38-6.99 (m, 8 H), 6.84 (d, 7 Hz, 1 H), 5.28-5.05 (m, 2 H), 4.80-4.52 (m, 1 H), 4.09 (m, 3 H), 3.59 (m, 1 1/2 H), 3.34 (m, 1 1/2 H), 3.24 (m, 1 H), 2.98 (m, 1 H), 2.70-2.48 (m, 2 1/2 H), 1.70-1.55 (m, 1 1/2 H), 1.61 (s, 3 H), 1.60 (s, 3 H), 1.22 (t, 7 Hz, 3 H), 1.00 (m, 1/2 H), 0.57 (m, 1/2 H).

FAB-MS: 562.3 (M+1)

The compounds shown in Table B9 were prepared according to the above procedure shown in Example B59.

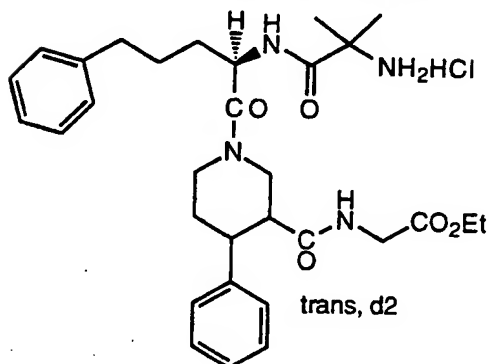
TABLE B9



| | | R | FAB-MS (M+1) |
|----|---|----|------------------------------------|
| 25 | 1 | d2 | β -alanine ethyl ester 576.3 |
| | 2 | d2 | L-alanine methyl ester 562.3 |

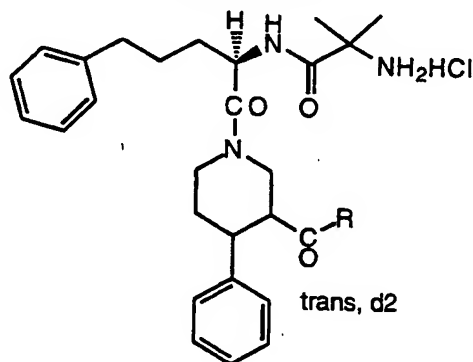
30

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EXAMPLE B60 (trans, d2)

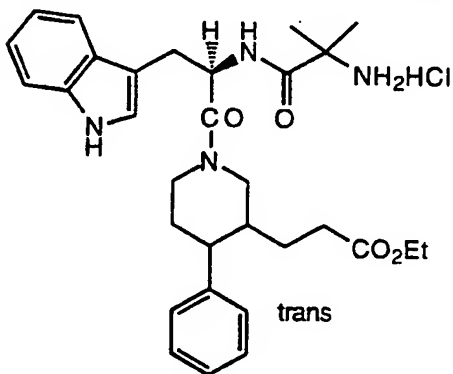
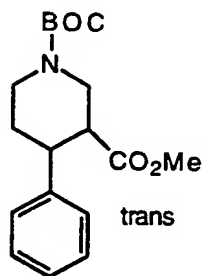
The intermediate prepared in Example B59, Step C (8 mg) in ethyl acetate was treated with HCl(g) at 0°C for 15 seconds and maintained at room temperature for 30 minutes, concentrated to dryness to give the crude material. To this crude material in 1 ml of chloroform was added intermediate 3 (8 mg), EDC (8 mg), HOBt (5 mg) and triethylamine (8 ml). The reaction was stirred at room temperature for 12 hours and poured into water. The mixture was extracted with methylene chloride and dried over sodium sulfate. Concentration and purification (PLC, hexanes/ethyl acetate=1/2) gave the desired product which was treated with HCl(gas) in EtOAc to provide the title compound (11 mg). FAB-MS: 551.4 (M+1)

The compounds shown in Table B10 were prepared according to the above procedure (coupled with different amino acids).

TABLE B10

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| | R | FAB-MS (M+1) |
|------|------------------------------|--------------|
| 1 d2 | β -alanine ethyl ester | 565.4 |
| 2 d2 | L-alanine methyl ester | 551.4 |

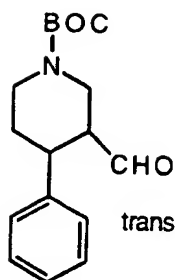
EXAMPLE B61 (trans, d1+d2)Step A:

To a solution of the intermediate prepared in Example B12, Step A (200 mg) in methanol was added a catalytic amount of sodium methoxide in methanol and refluxed for a couple of hours. The mixture was poured into 0.1 N hydrochloric acid and extracted with ether. The organic layer was dried over sodium sulfate, filtered and concentrated to give the desired product (190 mg).

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Step B:

5



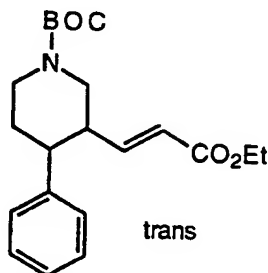
10

To a solution of the intermediate from Step A (120 mg) in 2 ml of toluene was added diisobutylaluminum hydride (1N in hexanes, 0.49 ml) at -78°C. After the reaction was stirred at -78°C for 1 hour it was quenched with methanol and then poured into 0.5 N hydrochloric acid solution. The mixture was extracted with ether. The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by PLC (hexanes/ethyl acetate=3/1) to give the desired product (60 mg).

15

Step C:

20

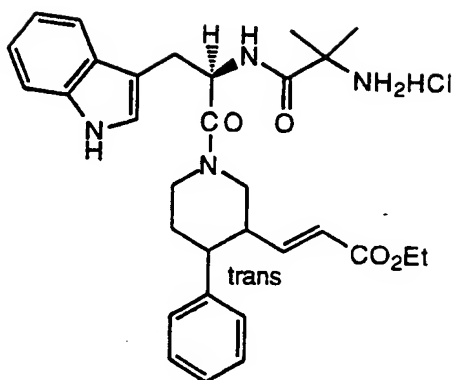


25

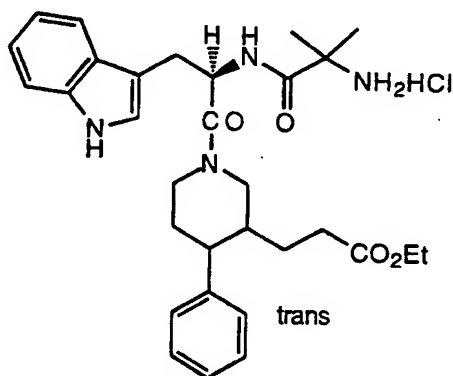
To a solution of triethyl phosphonoacetate in THF (5 ml) was added potassium bis(trimethylsilyl)amide (0.5 N in toluene, 1.45 ml) at 0°C. After 1 hour at room temperature the intermediate from Step B (42 mg) in THF (1 ml) was added to the phosphorane solution and refluxed for an hour. This mixture was concentrated and the residue was purified by PLC (hexanes/ethyl acetate=4/1) to give the desired product (50 mg).

30

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Step D:

To the intermediate prepared in Step C (50 mg) was added 0.5 ml of TFA at room temperature. After 10 minutes, the mixture was concentrated and azeotroped with toluene (3X). To a solution of the residue in 1 ml of chloroform was added Intermediate 1 (62 mg), EDC (53 mg), HOBt (23 mg) and triethylamine (58 ml). The mixture was stirred at room temperature for 3 hours and poured into water. The mixture was extracted with methylene chloride, and dried over sodium sulfate. Purification (PLC, hexanes/ethyl acetate=1/1) of the residue gave the coupled product (65 mg).

Step E:

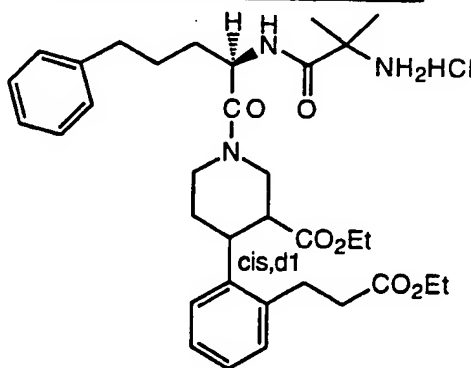
A solution of the intermediate prepared from Step D (50 mg) in methanol was hydrogenated with Pd(OH)₂/C at one atmosphere for a couple of hours. The mixture was filtered through Celite and the filtrate

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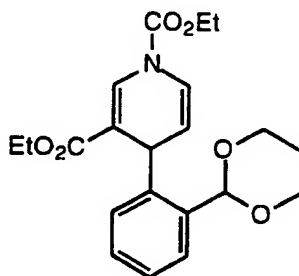
was concentrated. The residue was treated with HCl(gas) in EtOAc to give the desired product (36 mg).

FAB-MS: 533.3 (M+1)

EXAMPLE B62 (cis, d1)

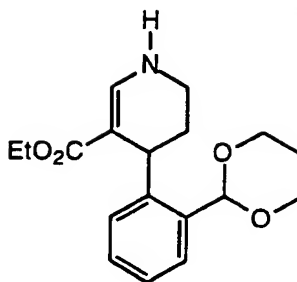


Step A:

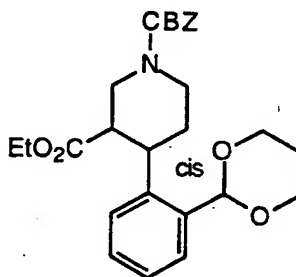


Ethyl chloroformate (12.9 ml) was added to a stirred suspension of cuprous chloride (1.35 g) in THF (200 ml). At 0°C, a solution of ethyl nicotinate was added slowly followed by the addition of Grignard reagent (prepared from 2-bromobenzaldehyde (25 g), 1,3-propanediol (20 ml), and magnesium (4.9 g) by the procedure described in *J. Org. Chem.*, 51,3490 (1986)). The reaction was stirred for an hour and poured into a saturated ammonium chloride/ammonia solution (1/1) and extracted with ethyl acetate. The organic layer was washed with 1 N hydrochloric acid and brine and dried over sodium sulfate. Evaporation of the solvent gave the desired product. Crystallization of this material from ethyl acetate gave 25g of the desired material.

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Step B:

The intermediate prepared in Step A (25 g) was dissolved in hot ethyl acetate (500 ml) and then cooled down to room temperature. This organic solution was hydrogenated with PtO₂ at one atmosphere for a couple of hours (monitored by TLC). The mixture was filtered through Celite and the filtrate concentrated under vacuum. The residue was dissolved in hot ethanol (150 ml) was treated with 6N NaOH (75 ml) at reflux for 10 minutes. The mixture was concentrated under vacuum and to the residue was added water and stirred at room temperature for 10 minutes. The pale white solid was collected by filtration. The filtrate was extracted with methylene chloride and washed with brine and dried over sodium sulfate. The solvent was concentrated and combined with pale white solid to give 13.6 g of desired product.

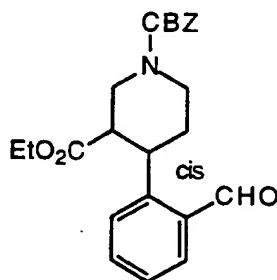
Step C:

To a solution of the intermediate prepared in Step B (10.1 g) in THF (300 ml) at 0°C was added a catalytic amount of indicator (bromocresol green) and NaCNBH₃ (64 mmole). To this reaction mixture was added 1 N hydrochloric acid till a yellow color persisted (pH=4.0). After an hour, the mixture was poured into 1 N NaOH and extracted with chloroform. The organic layer was washed with brine

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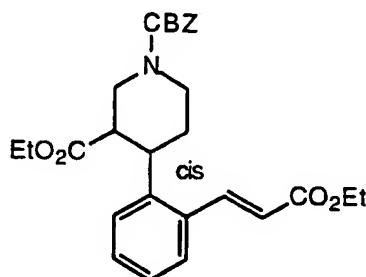
dried over sodium sulfate and concentrated. The residue was purified by filtration through silica gel with methylene chloride/methanol=10/1 to remove very polar material. The material obtained after concentration of the filtrate was dissolved in chloroform and to this mixture was added triethylamine (6 ml) and CBZ-Cl (4.6 ml) at 0°C. After stirring for 15 minutes, the reaction was poured into water and extracted with methylene chloride. The organic layer was washed with brine, dried over sodium sulfate. Concentration and purification (MPLC, hexanes/ethyl acetate=5/1) gave the desired product (6.4 g).

Step D:



To a solution of the intermediate prepared from Step C (2.17 g) in methanol (30 ml) was added 1 N hydrochloric acid (5 ml) and stirred for an hour. The mixture was poured into 1N NaOH solution and extracted with ether. The organic layer was washed with brine and dried over magnesium sulfate. Purification of the residue (chromatatron, hexanes/ethyl acetate=5/1) gave the desired product (1.56 g).

Step E:

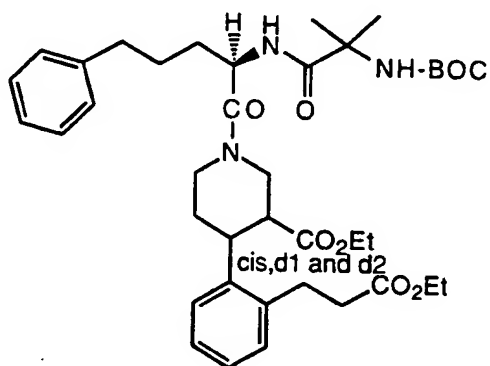


To a solution of triethyl phosphonoacetate in THF (25 ml) was added potassium bis(trimethylsilyl)amide (0.5 N in toluene, 4.56 ml)

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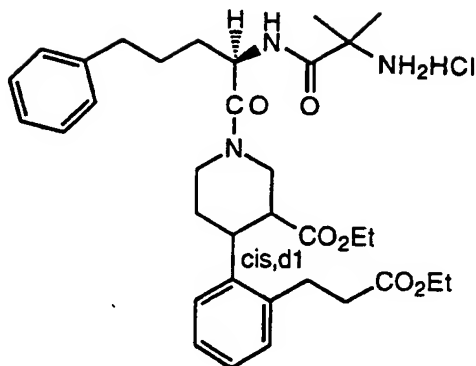
at 0°C. After stirring an hour at room temperature the intermediate from Step D (860 mg) in THF (10 ml) was added to the phosphorane solution at room temperature. The mixture was stirred at room temperature for an hour and then quenched with 1 N hydrochloric acid. This mixture was extracted with ether, washed with brine, and dried over magnesium sulfate. Purification of the residue (chromatatron, hexanes/ethyl acetate=5/1) gave the desired product (873 mg).

Step F:



The intermediate prepared in Step E (870 mg) was dissolved in methanol and hydrogenated with Pd(OH)₂/C at one atmosphere for one and one-half hours. The mixture was filtered through Celite and the filtrate was concentrated under vacuum. To the residue in chloroform was added intermediate 3 (749 mg), EDC (714 mg) and HOBt (276 mg) and stirred for 2h. The mixture was concentrated and purified (chromatatron, hexanes/ethyl acetate=2/1) to give two diastereomers (545 mg, the less polar diastereomer, d1; 500 mg the more polar diastereomer, d2).

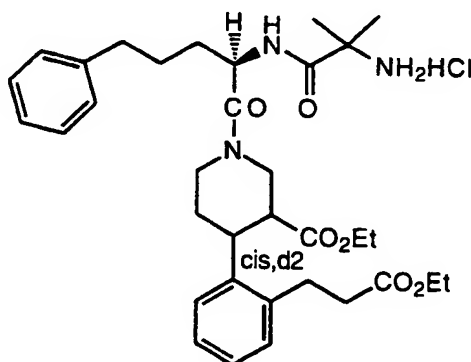
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Step G:

To a solution of the less polar diastereomer prepared in Step F (200 mg) in ethyl acetate was bubbled in HCl(g) at 0°C for 15 seconds. After standing for 30 minutes at room temperature the mixture was concentrated and purified (LH-20, 100% methanol) to give the cis, d1 product as a white solid (100 mg).

¹H NMR (400 MHz, CD₃OD, mixture rotamers): 7.28-7.06 (m, 9 H), 5.09 (m, 1/2 H), 4.85-4.55 (m, 1 1/2 H), 4.17 (m, 1 H), 4.10 (q, 7 Hz, 2 H), 3.77 (m, 2 H), 3.46 (m, 1 1/2 H), 3.25 (m, 1/2 H), 3.15-2.39 (m, 9H), 1.89-1.60 (m, 5 H), 1.65 (s, 2 H), 1.62 (s, 2 H), 1.57 (s, 2 H), 1.21 (t, 7 Hz, 3 H), 0.91 (t, 7 Hz, 3/2 H), 0.85 (t, 7 Hz, 3/2 H).

FAB-MS: 594.3 (M+1)

EXAMPLE B63 (cis, d2)

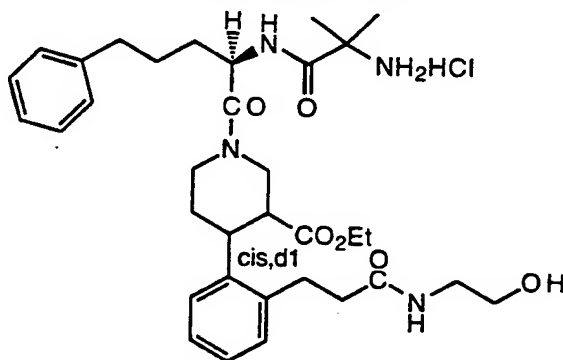
- 236 -

The desired cis, d2 product (3.3 mg) was obtained from the more polar diastereomer obtained in Example B62, Step F by the procedure described in Example B62, Step G.

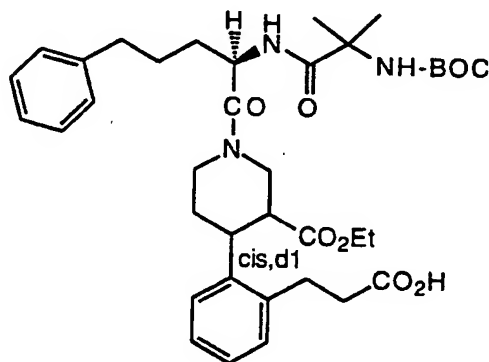
¹H NMR (400 MHz, CD₃OD, mixture rotamers): 7.90-7.03 (m, 9 H), 4.92-4.61 (m, 2 H), 4.10 (q, 7 Hz, 2 H), 4.07 (m, 1 H), 3.79 (m, 2 H), 3.45 (m, 1 1/2 H), 3.25 (m, 1/2 H), 3.07-2.38 (m, 9H), 1.94-1.69 (m, 4 H), 1.63 (s, 3/2 H), 1.61 (s, 3/2 H), 1.60 (s, 3/2 H), 1.59 (s, 3/2 H), 1.20 (t, 7 Hz, 3 H), 0.91 (t, 7 Hz, 3 H).

FAB-MS: 594.3 (M+1).

EXAMPLE B64 (cis, d1)



Step A:

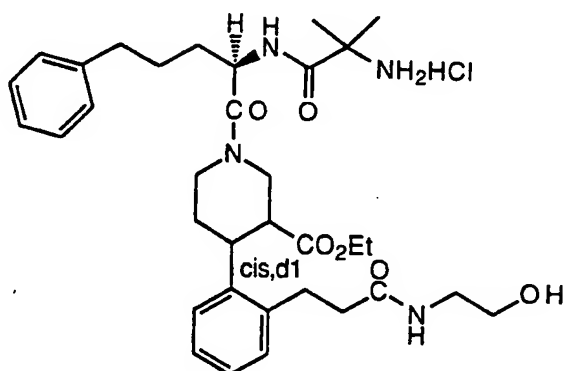


To the less polar diastereomer prepared in Example B62, Step F (30 mg) in ethanol (1 ml) was added 6 N NaOH (30 ml) at room temperature. After stirring for an hour the mixture was concentrated. To the residue was added 1 N hydrochloric acid and extracted with ethyl

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acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated to give the desired product (20 mg).

Step B:

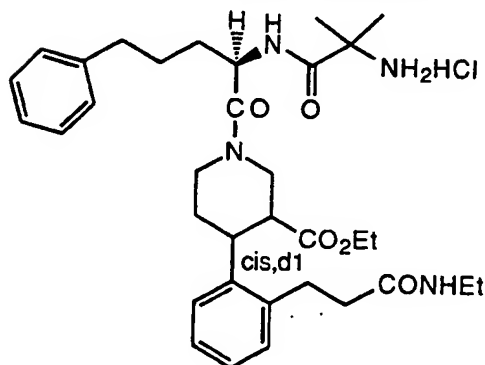


To a solution of the intermediate prepared in Step A (6 mg) in 0.5 ml of chloroform was added ethanolamine (0.8 ml), EDC (3.5 mg), and HOBt (1.8 mg). The reaction was stirred at room temperature for a couple of hours and poured into water. The mixture was extracted with methylene chloride and dried over sodium sulfate. Concentration and purification (PLC, methylene chloride/methanol=20/1) provided the coupled product. This material was deprotected with HCl in EtOAc to give the desired cis, d1 product (1.6 mg).

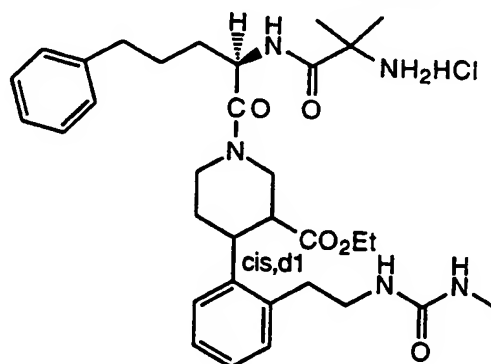
^1H NMR (400 MHz, CD_3OD , mixture rotamers): 7.28-7.07 (m, 9 H), 5.09 (m, 1/2 H), 4.85-4.62 (m, 1 1/2 H), 4.19 (m, 1 H), 3.75 (m, 2 H), 3.55 (t, 6 Hz, 2 H), 3.45 (m, 1 H), 3.34-2.84 (m, 6 1/2 H), 2.73-2.45 (m, 5 1/2 H), 1.85-1.57 (m, 5 H), 1.65 (s, 3/2 H), 1.62 (s, 3/2 H), 1.57 (s, 3/2 H), 1.56 (s, 3/2 H), 0.92 (t, 7 Hz, 3/2 H), 0.85 (t, 7 Hz, 3/2 H).

FAB-MS: 609.2 (M+1)

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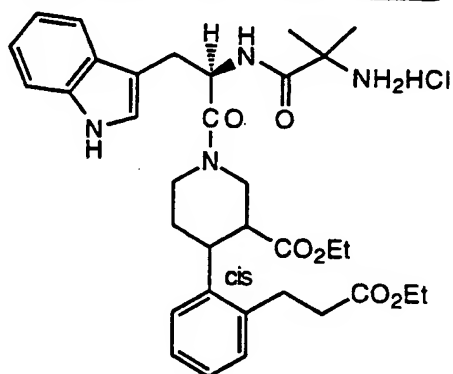
EXAMPLE B65 (cis, d1)

To a solution of the intermediate prepared in Example B64 Step A (6 mg) in 0.5 ml of chloroform was added ethylamine hydrochloride salt (1 mg), EDC (3.5 mg), triethylamine (4 ml) and HOBt (1.8 mg). The reaction was stirred at room temperature for a couple of hours and poured into water, and extracted with methylene chloride and dried over sodium sulfate. Purification of the residue (PLC, methylene chloride/methanol=20/1) gave the coupled product. This material was treated with HCl in EtOAc to yield the desired cis, d1 product (1.5 mg). ¹H NMR (400 MHz, CD₃OD, mixture rotamers): 7.28-7.07 (m, 9 H), 5.09 (m, 1/2 H), 4.83-4.62 (m, 1 1/2 H), 4.17 (m, 1 H), 3.75 (m, 2 H), 3.50 (m, 1 1/2 H), 3.25-2.84 (m, 6 1/2 H), 2.72-2.39 (m, 5 H), 1.89-1.58 (m, 5 H), 1.65 (s, 3/2 H), 1.61 (s, 3/2 H), 1.57 (s, 3/2 H), 1.56 (s, 3/2 H), 1.06 (t, 7 Hz, 3 H), 0.91 (t, 7 Hz, 3/2 H), 0.85 (t, 7 Hz, 3/2 H). FAB-MS: 593.3 (M+1)

EXAMPLE B66 (cis, d1)

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To a solution of the intermediate prepared from Example B64, Step A (8 mg) in methylene chloride (1 ml) was added ethyl chloroformate (2.3 ml) and triethylamine (5 ml) at 0°C. The reaction mixture was stirred at 0°C for 10 minutes and room temperature for an hour. The mixture was poured into saturated sodium bicarbonate and extracted with methylene chloride. The organic layer was washed with brine and dried over sodium sulfate, and concentrated. To the residue in acetone (0.5 ml) was added sodium azide (2.3 mg) in water (0.2 ml) at 0°C. After stirring at room temperature for an hour the mixture was extracted with ether, washed with water and brine, and dried over MgSO₄. Filtration and evaporation gave acyl azide which was dissolved in toluene (1 ml) and refluxed for 3 hours to give the isocyanate. The toluene solution was cooled down to room temperature and methylamine (40% in water, 9 ml) was added. After stirring for 12 hours in room temperature, the reaction was quenched with 1 N HCl and extracted with methylene chloride and then dried over sodium sulfate and concentrated. Purification of the residue (PLC, methylene chloride/methanol=20/1) gave desired urea which was deprotected with HCl in EtOAc to yield the desired product (3.5 mg).
FAB-MS: 594.3 (M+1).

EXAMPLE B67 (cis, d1+d2)

The intermediate prepared in Example B62, Step E (17 mg) was dissolved in methanol and hydrogenated with Pd(OH)₂/C at one atmosphere for one and half hours. The mixture was filtered through Celite and the filtrate was concentrated under vacuum to give the free

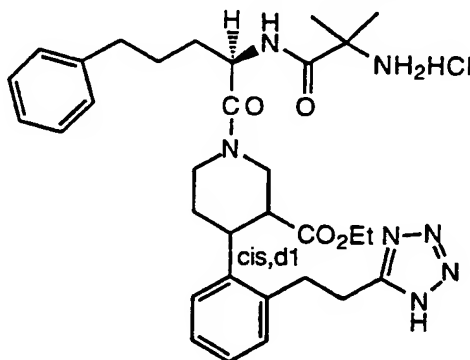
- 240 -

amine (11 mg). To this free amine (5.5 mg) in chloroform was added Intermediate 1 (7 mg), EDC (6 mg) and HOBt (4 mg). After 12 hours, the mixture was concentrated and purified (chromatatron, hexanes/ethyl acetate=2/1) to give an inseparable mixture of diastereomers. This

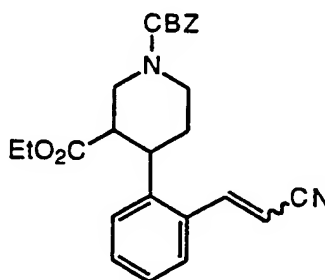
diastereomeric mixture in ethyl acetate was treated with HCl(g) at 0°C for 15 seconds. After standing for 30 minutes at room temperature, the mixture was concentrated to give a white solid (8 mg).

FAB-MS: 605.3 (M+1)

EXAMPLE B68 (cis, d1)



Step A:

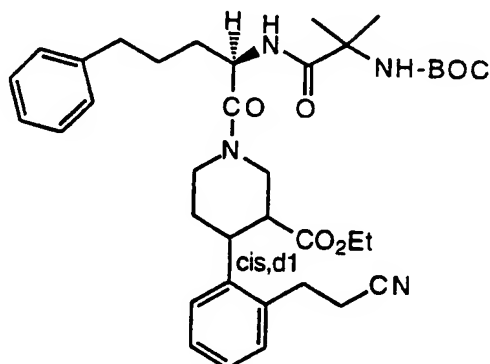


To a solution of diethyl cyanomethyl phosphonate in THF (25 ml) was added potassium bis(trimethylsilyl)amide (0.5 N in toluene, 3.44 ml) at 0°C. After stirring an hour at room temperature the intermediate from Example B62, Step D (650 mg) in THF (10 ml) was added to the phosphorane solution at room temperature. The mixture was stirred at room temperature for an hour and then quenched with 1 N hydrochloric acid. This mixture was extracted with ether and washed with brine, and dried over magnesium sulfate and concentrated.

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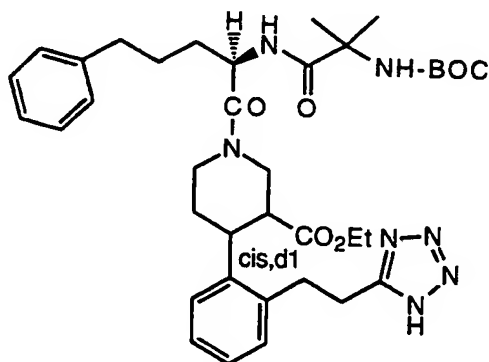
Purification (chromatatron, hexanes/ethyl acetate=5/1) gave the α,β -unsaturated nitrile (trans, 466 mg; cis, 124 mg).

Step B:



The intermediate prepared in Step A (590 mg) was dissolved in methanol and hydrogenated with $\text{Pd}(\text{OH})_2/\text{C}$ at one atmosphere for one and half hours. The mixture was filtered through Celite and the filtrate was concentrated under vacuum. To the residue in chloroform was added intermediate 3 (560 mg), EDC (560 mg) and HOBT (208 mg). After a couple of hours, the mixture was concentrated and purified (chromatatron, hexanes/ethyl acetate=1/1) to give two diastereomers (220 mg, the less polar diastereomer, d1; 260 mg the more polar diastereomer, d2).

Step C:

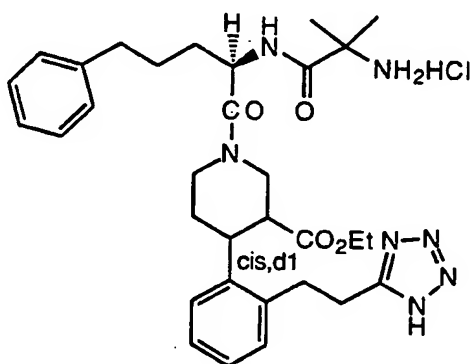


To the less polar diastereomer prepared in Step B (220 mg) in toluene (5 ml) was added trimethyltin azide (206 mg) and refluxed for

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6 1/2 hours. The solvent was removed under vacuum. The residue was redissolved in methylene chloride/methanol/acetic acid=20/1/0.1 (20 ml) and allowed to stand at room temperature for 12 hours and the solvent was removed under vacuum. The residue was purified by PLC
5 (methylene chloride/methanol/acetic acid=20/1/0.1) to give the desired product (120 mg).

Step D:



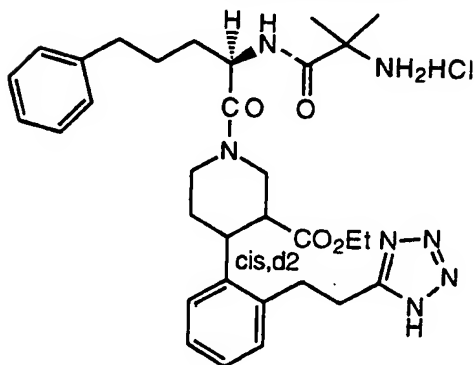
The intermediate in Step C (120 mg) was treated with HCl in EtOAc to give the desired cis, d1 product as a white solid (98 mg).

20 ¹H NMR (400 MHz, CD₃OD, mixture of rotamers): 7.28-7.08 (m, 9 H), 5.08 (m, 1/2 H), 4.84-4.53 (m, 1 1/2 H), 4.18 (m, 1 H), 3.78 (m, 3 H), 3.27-3.03 (m, 6 H), 2.85-2.30 (m, 4 H), 1.90-1.38 (m, 5 H), 1.65 (s, 3/2 H), 1.61 (s, 3/2 H), 1.57 (s, 3/2 H), 1.56 (s, 3/2 H), 0.90 (t, 7 Hz, 3/2 H), 0.85 (t, 7 Hz, 3/2 H).

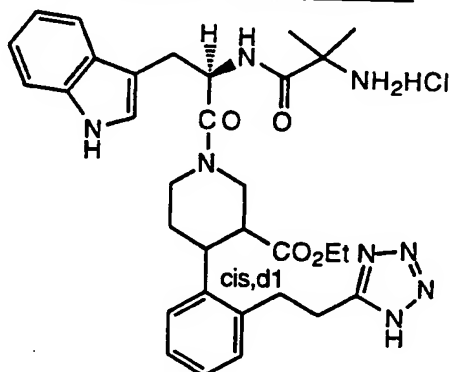
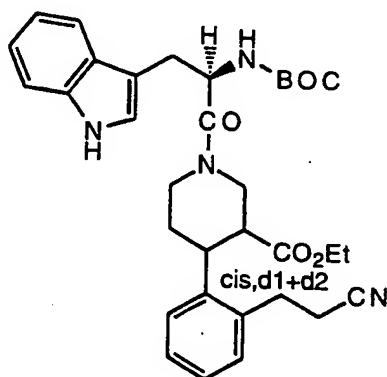
25 FAB-MS: 590.2 (M+1).

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EXAMPLE B69 (cis, d2)

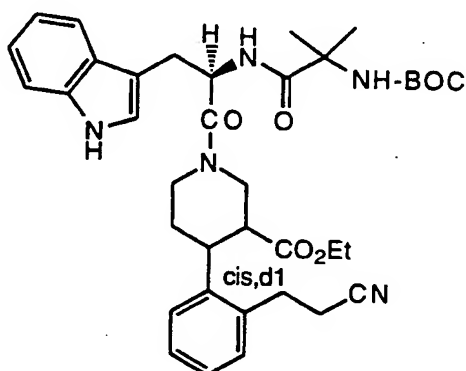
The desired product (2 mg) was prepared from the more polar diastereomer (6.8 mg) obtained in Example B68, Step B by the procedure described in Example B68, Step C and D.
FAB-MS: 590.4 (M+1).

EXAMPLE B70 (cis, d1)Step A:

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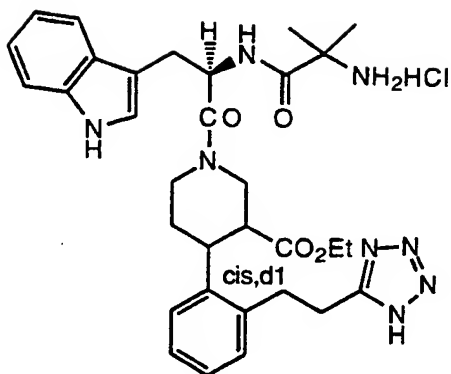
The intermediate prepared in Example B68, Step A (782 mg) was dissolved in methanol and hydrogenated with Pd(OH)₂/C at one atmosphere for one and one-half hours. The mixture was filtered through Celite and the filtrate was concentrated under vacuum. To the residue in chloroform was added Boc-D-Tryptophan (468 mg), EDC (534 mg) and HOBt (207 mg). After a couple of hours, the mixture was concentrated and purified (MPLC, hexanes/ethyl acetate=1/1) to give two diastereomers (316 mg, the less polar diastereomer, d1; 300 mg the more polar diastereomer, d2).

Step B:



The less polar diastereomer from Step A (316 mg) in ethyl acetate was treated with HCl(g) at 0°C for 15 seconds. After standing 30 minutes at room temperature, the mixture was concentrated to give crude material. To the residue in 5 ml of chloroform was added N-Boc-a-methylalanine (158 mg), EDC (149 mg), triethylamine (217 ml) and HOBt (77 mg) and stirred for 12 hours at room temperature. The mixture was poured into water and extracted with methylene chloride and washed with brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by chromatatron (hexanes/ethyl acetate=1/2) to give the desired compound (287 mg).

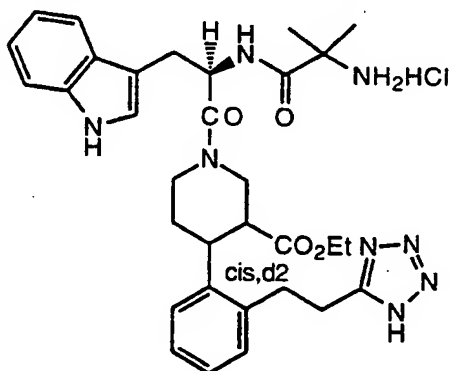
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Step C:

The desired cis, d1 product (135 mg) was prepared from above intermediate (287 mg) prepared in Example B70, Step B by the procedure described in Example B68, Steps C and D.

¹H NMR (400 MHz, CD₃OD, mixture rotamers): 8.09 (d, 8 Hz, 1/2 H), 7.80 (d, 8 Hz, 1/2 H), 7.64 (d, 8 Hz, 1/2 H), 7.57 (d, 8 Hz, 1/2 H), 7.35 (d, 7 Hz, 1 H), 7.22-7.00 (m, 7 H), 5.31-5.20 (m, 1 H), 4.71 (d, 12 Hz, 1/2 H), 4.41 (d, 12 Hz, 1/2 H), 4.15 (m, 1/2 H), 3.92-3.67 (m, 2 1/2 H), 3.43-3.03 (m, 8 1/2 H), 2.80 (m, 1 H), 2.52-2.25 (m, 1 1/2 H), 1.59 (s, 3/2 H), 1.54 (s, 3/2 H), 1.50 (s, 3/2 H), 1.35 (3/2 H), 1.43 (m, 1 H), 0.93 (t, 7 Hz, 3/2 H), 0.84 (t, 7 Hz, 3/2 H).

FAB-MS: 601.1 (M+1).

EXAMPLE B71 (cis, d2)

The title product (125 mg) was prepared from the more polar diastereomer (300 mg) prepared in Example B70, Step A by the

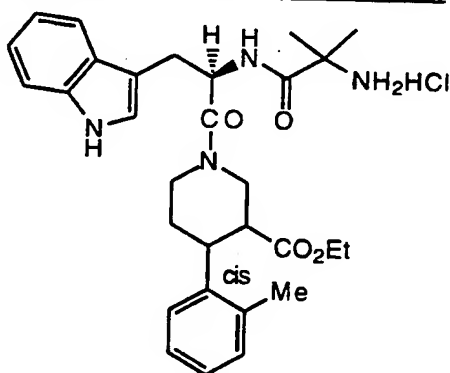
- 246 -

procedure described in Example B70, Step B and Example B68, Steps C and D.

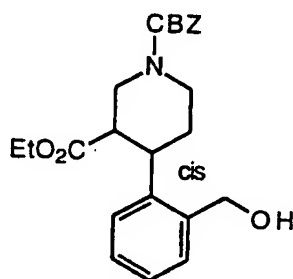
¹H NMR (400 MHz, CD₃OD, mixture rotamers): 8.24 (d, 8 Hz, 1/2 H), 8.09 (d, 8 Hz, 1/2 H), 7.59 (d, 8 Hz, 1/2 H), 7.54 (d, 8 Hz, 1/2 H), 7.34-6.92 (m, 8 H), 5.40 (m, 1/2 H), 5.15 (m, 1/2 H), 4.64 (d, 13 Hz, 1/2 H), 4.55 (d, 13 Hz, 1/2 H), 4.22 (m, 1/2 H), 4.09 (m, 1/2 H), 3.81-3.58 (m, 2 1/2 H), 3.40-2.84 (m, 9 1/2 H), 2.71-2.32 (m, 1 1/2 H), 1.63 (s, 3/2 H), 1.52 (s, 3/2 H), 1.48 (s, 3/2 H), 1.29 (3/2 H), 1.53 (m, 1/2 H), 1.32 (m, 1/2 H), 0.90 (t, 7 Hz, 3/2 H), 0.79 (t, 7 Hz, 3/2 H).

FAB-MS: 601.2 (M+1).

EXAMPLE B72 (cis, d1+d2)



Step A:

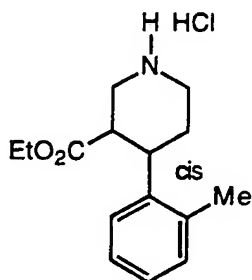


To a solution of the intermediate prepared in Example B62, Step C (235 mg) in methanol (3 ml) was added 1 N hydrochloric acid (0.5 ml) and stirred for an hour. To the resulting mixture was added NaCNBH₃ (1.0 N in THF, 0.7 ml) and after 5 minutes the reaction mixture was poured into 1 N hydrochloric acid and extracted with ether. The organic layer was washed with brine, dried over sodium sulfate and

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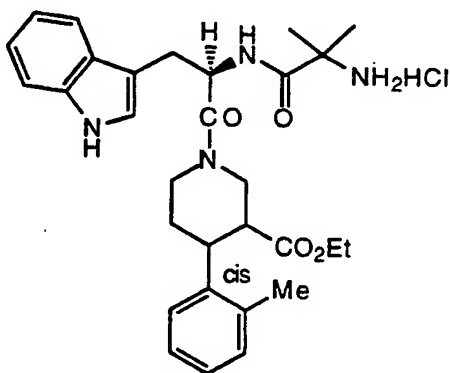
concentrated. The residue was purified (chromatatron, hexanes/ethyl acetate=1/1) to give the desired product (142 mg).

Step B:



To a solution of the intermediate prepared in Step A (142 mg) in methanol was added HCl in ether and Pd(OH)₂ and stirred under an hydrogen atmosphere for 12 hours. The mixture was filtered through Celite and the filtrate was concentrated to give the desired product (105 mg).

Step C:

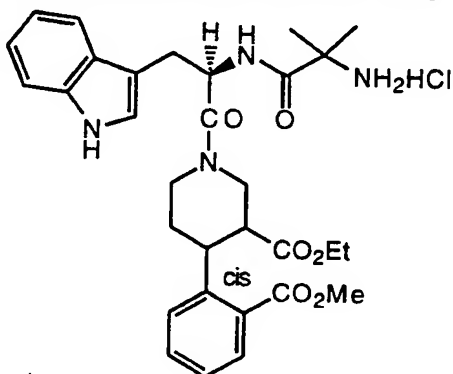


To the intermediate (105 mg) prepared in Step B in 2 ml of chloroform was added Intermediate 1 (81 mg), EDC (54 mg), HOBt (28 mg) and triethylamine (53 ml) and the reaction was stirred at room temperature for 12 hours and poured into water. The mixture was extracted with methylene chloride, dried over sodium sulfate and concentrated. Purification of the residue (chromatatron, hexanes/ethyl acetate=1/1) gave the desired product which was treated with HCl in EtOAc to give the desired product (56 mg).

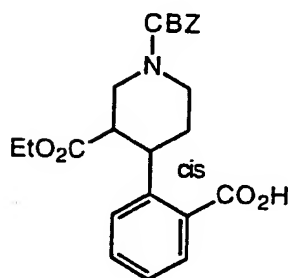
- 248 -

FAB-MS: 519.2 (M+1)

EXAMPLE B73 (cis, d1+d2)

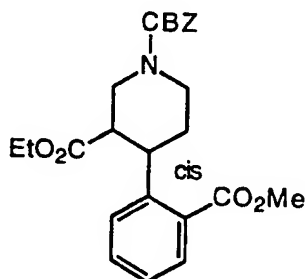


Step A:



To the intermediate prepared in Example B72, Step A (100 mg) at 0°C in acetone was added Jones reagent (4 N, 0.2 ml). After stirring for 16 hours in room temperature the mixture was quenched with isopropanol, filtered through celite. The filtrate was extracted with ethyl acetate. The organics were washed with brine and dried over sodium sulfate and concentrated to give the desired product (100 mg).

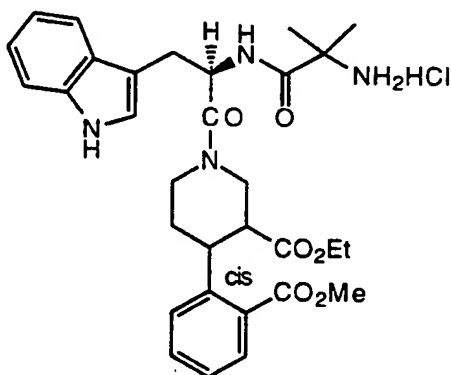
Step B:



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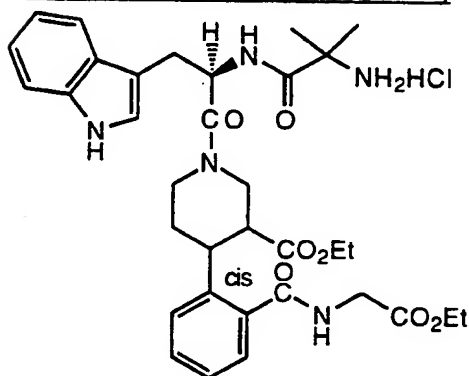
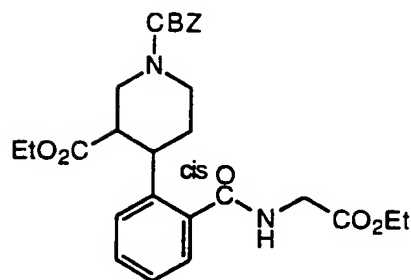
To the intermediate prepared in Step A (50 mg) in ether at 0°C was added diazomethane (Blatt, Org. Syn. Collective Vol. 4, p225). The mixture was slowly warmed up to room temperature and stirred for 12 hours. Concentration and purification of the residue (PLC, hexanes/ethyl acetate=3/1) gave the desired product (50 mg).

Step C:

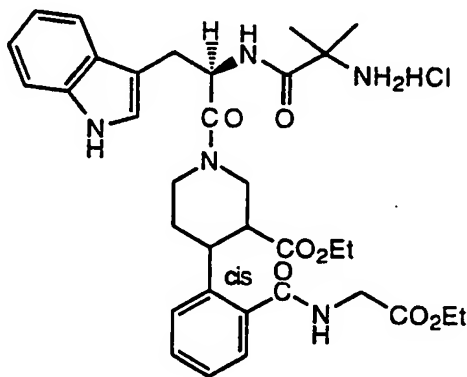


The intermediate prepared in Step B (50 mg) was dissolved in methanol and hydrogenated over Pd(OH)₂/C at one atmosphere for one and half hours. The mixture was filtered through Celite and the filtrate was concentrated under vacuum. To the residue in chloroform was added intermediate 1 (48 mg), EDC (45 mg) and HOBt (24 mg). After a couple of hours, the mixture was concentrated and purified (chromatatron, hexanes/ethyl acetate=1/1) to give the coupled product. Deprotection of this material by the HCl/EtOAc protocol gave the desired product (47 mg).
FAB-MS: 563.1 (M+1)

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EXAMPLE B74 (cis, d1+d2)Step A:

To the intermediate prepared in Example B73, Step A (50 mg) in chloroform was added glycine ethyl ester HCl salt (51 mg), EDC (46 mg) triethylamine (84 ml), and HOBt (32 mg). The reaction was stirred at room temperature for 12 hours and poured into water. The mixture was extracted with methylene chloride and dried over sodium sulfate, concentrated and purified (PLC, hexanes/ethyl acetate=1/1) to give the coupled product (45 mg).

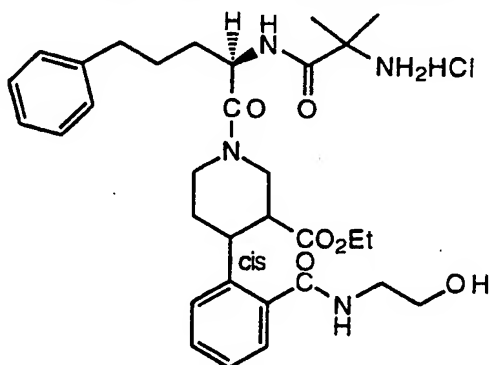
Step B:

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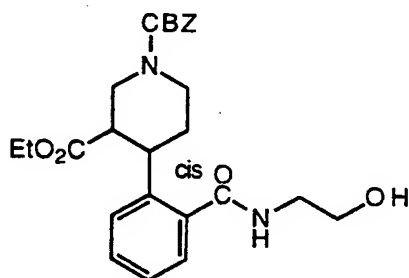
The title product (43 mg) was prepared from the intermediate (45 mg) obtained in Step A by the procedure desired in Example B73, Step C.

FAB-MS: 634.2 (M+1).

EXAMPLE B75 (cis, d1+d2)



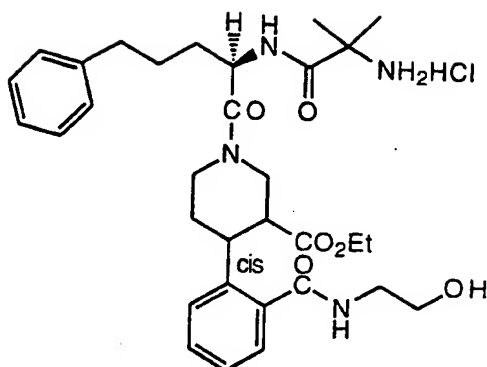
Step A:



To intermediate prepared in Example B73, Step A (53 mg) in chloroform was added ethanolamine (12 ml), EDC (37 mg) and HOBt (19 mg) and stirred at room temperature for 12 hours and poured into water. The mixture was extracted with methylene chloride and dried over sodium sulfate and concentrated. The residue was purified (chromatatron, methylene chloride/methanol=20/1) to give the coupled product (29 mg).

Step B:

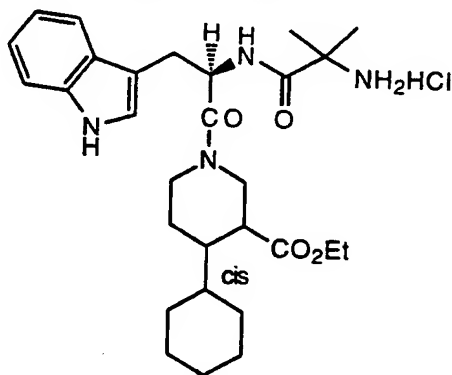
- 252 -



The desired product (16.8 mg) was prepared from the above intermediate (29 mg) by the procedure described in Example B62, Steps F and G.

FAB-MS: 581.2 (M+1).

EXAMPLE B76



To a solution of the intermediate prepared in Example B12, Step A-1 (100 mg) in acetic acid was added PtO₂ and hydrogenated at one atmosphere for 24 hours (monitored by TLC). The mixture was filtered through Celite, the filtrate was concentrated and the residue was azeotroped with toluene. The residue was dissolved in TFA and stirred for 20 minutes at room temperature. The reaction mixture was concentrated and the residue was dissolved in methylene chloride (0.5 ml) and was reacted with intermediate 1 (15 mg), EDC (15 mg), HOBt (6 mg) and triethylamine (11 ml). The mixture was stirred at room temperature for 3 hours and poured into water. The mixture was extracted with methylene chloride, dried over sodium sulfate and

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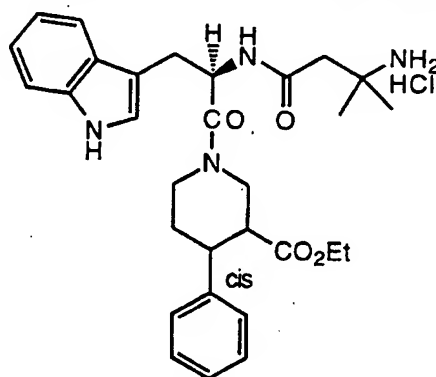
concentrated. Purification of the residue (PLC, hexanes/ethyl acetate=1/1) gave the coupled product which was treated with HCl in EtOAc to yield the desired product (8 mg).

FAB-MS: 511.1 (M+1)

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EXAMPLE B77 (cis, d1+d2)

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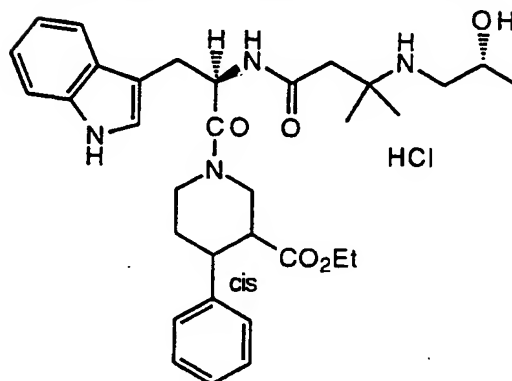
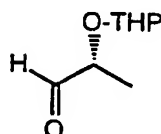


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The intermediate prepared in Example B12, Step B was dissolved in methanol and hydrogenated over Pd(OH)₂ at one atmosphere for a couple of hours. The mixture was filtered through celite and the filtrate was concentrated under vacuum. To the residue (88 mg) in chloroform (1 ml) was added N-Boc-β,β-dimethyl-β-alanine (48 mg, W.R. Schoen etc., *J. Med. Chem.*, **37**, 897 (1994)), EDC (48 mg), and HOBt (30 mg), stirred for 12 hours and the mixture was poured into water. The mixture was extracted with methylene chloride, dried over sodium sulfate and concentrated. Purification of the residue (chromatatron, hexanes/ethyl acetate=1/1) gave the coupled product that was deblocked with HCl in EtOAc to give the desired product (58 mg). FAB-MS: 519.2 (M+1)

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EXAMPLE B78 (cis, d1+d2)Step A:

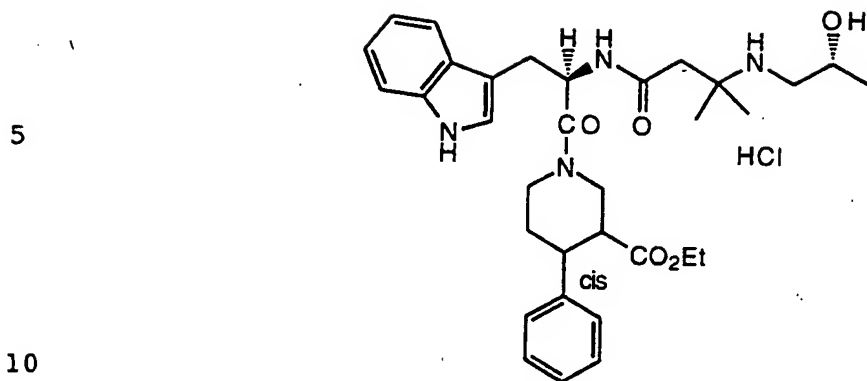
To a solution of methyl (R)-lactate (1 ml) in dihydropyran (5 ml) was added one drop of concentrated hydrochloric acid at room temperature. The reaction was stirred for an hour, concentrated and purified by chromatatron (hexanes/ethyl acetate=3/1) to give the desired product (1.49 g). To the THP protected lactate (500 mg) in toluene (10 ml) was added diisobutylaluminum hydride (1N in cyclohexane, 3.45 ml) at -78°C and after one and half hours, the reaction was quenched with methanol at low temperature. The mixture was poured into 5% aqueous citric acid and extracted with ether. The organic layer was washed with brine, dried over sodium sulfate and concentrated to give the protected aldehyde.

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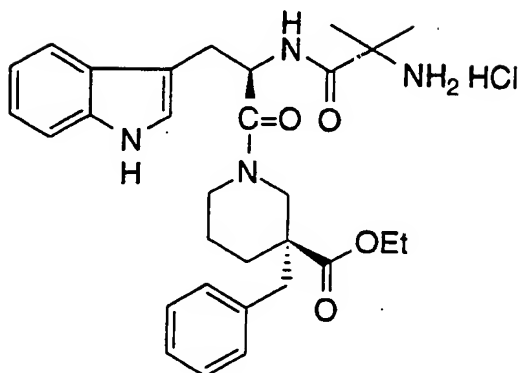
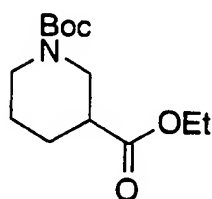
Step B:

To a solution of the product (25 mg) prepared in Example B77 in methanol (0.5 ml) was added the intermediate (36 mg) prepared in Step A and sodium acetate (18 mg) and stirred at room temperature for an hour. To the mixture was added NaCNBH₃ (1N in THF, 90 ml) slowly and stirred for 16 hours and concentrated. The residue was purified by chromatatron (methylene chloride/methanol/ammonium hydroxide=10/1/0.1) to give the desired product which was dissolved in methanol (0.5 ml) and was treated with 9 N hydrochloric acid (0.2 ml). After stirring for 2 hours, the mixture was concentrated and dried to give the desired product (10.5 mg).
FAB-MS: 577.4 (M+1).

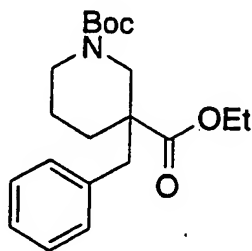
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EXAMPLE C1Step A:

To a stirred solution of ethyl nipecotate (15 g, 95.4 mmol) and DMAP (0.05 eq.) in dichloromethane at 0°C was added dropwise by an addition funnel di-tert-butyl dicarbonate (21.8 g, 100 mmol) in dichloromethane (200 mL). The mixture was stirred for 2-3 hours. The solution was washed with 3 N HCl and saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated to give the desired product (18.7 g, 88%).

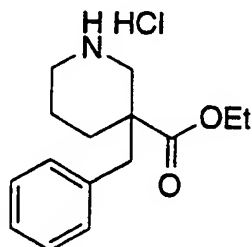
Step B:

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To a stirred solution of ethyl N-t-Boc nipecotate (7 g, 26.90 mmol) in THF (100 mL) at -78°C under argon was added LHMDS (28 mL, 28 mmol) over a 10 minute period. The solution was allowed to stir an additional 30 minutes at -78°C; then benzyl bromide (4.8 g, 28 mmol) was added slowly to the solution. The reaction mixture was stirred overnight and allowed to warm to room temperature. The material was concentrated, then diluted with water, and extracted using ethyl acetate (2 x 200 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by silica gel flash column chromatography, eluting with 20% ethyl acetate in hexane, provided the title compound. (8.32 g, 88%).

FAB-MS calc. for C₂₀H₂₉NO₄: 347; Found 348 (M+H)

Step C:

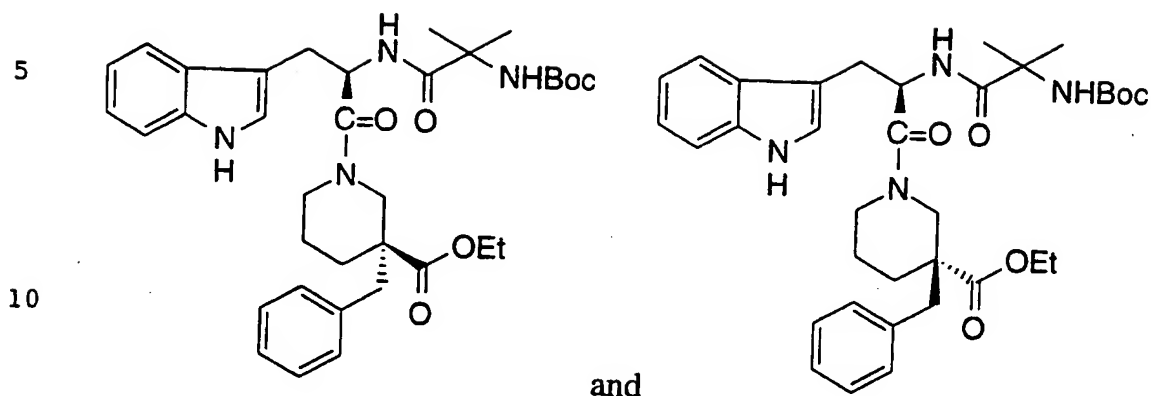


A solution of the intermediate from Step B (8 g, 23.02 mmol) in ethyl acetate (80 mL) was cooled to 0°C. While stirring, hydrogen chloride gas was bubbled into the mixture until saturation occurred. The reaction was stirred for 40 minutes, until TLC analysis indicated that the reaction was complete. The solution was then concentrated to remove the ethyl acetate to afford the product (6.53 g, 99%).

¹H NMR (CDCl₃, 400MHz) δ 7.25-7.19 (m, 3 H), 7.04-7.01 (m, 2 H), 5.35 (v. br. s, 2 H), 4.22-4.10 (m, 2 H), 3.44 (d, J = 13 Hz, 1 H), 3.21 (br. d, J = 12.7 Hz, 1 H), 2.95 (d, J = 13.5 Hz, 1 H), 2.76-2.68 (m, 3 H), 2.22 (br. d, J = 13 Hz, 1 H), 1.73-1.71 (m, 1 H), 1.61-1.48 (m, 2 H), 1.18 (t, J = 7 Hz, 3 H).

FAB-MS calc. for C₁₅H₂₁NO₂: 247; Found 248 (M+H)

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Step D:

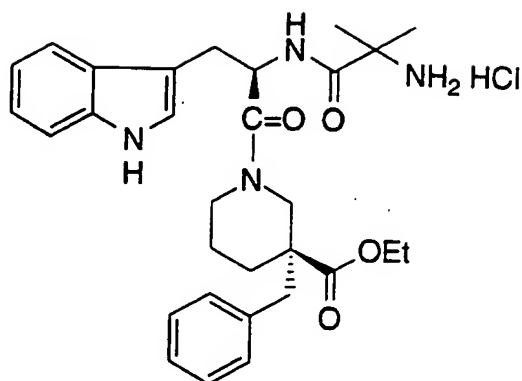
To a solution of the intermediate prepared in the previous step (1.2 g, 4.23 mmol), and Intermediate 1 (1 eq.), HOBT (1 eq.), and N-methyl morpholine (1 eq.) in dichloromethane cooled to 0°C was added EDC (1.5 eq.). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 40% ethyl acetate in hexane provided two enantiomerically pure compounds. The compound which came out first from the column was designated as d1 (1.14g), which has an R-absolute stereochemistry at the 3-position of the nipecotate; and the compound which came out of the column second was designated as d2 (1.08 g), which has an S-absolute stereochemistry (see Example C2 for assignment) at the 3-position of the nipecotate.

d1 FAB-MS calc. for C₃₅H₄₆N₄O₆: 618; Found 619 (M+H)
d2 FAB-MS calc. for C₃₅H₄₆N₄O₆: 618; Found 619 (M+H)

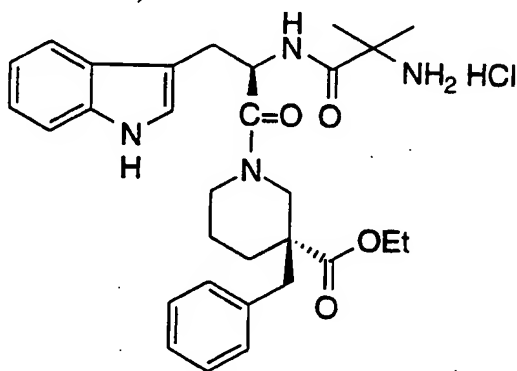
Step E:

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Prepared by the procedure described in Step C from the intermediates d1 from the previous step (1 g) in ethyl acetate (20 mL) and HCl gas at 0°C for 1.5 hours. Product : 860 mg, 91%.
FAB-MS calc. for C₃₀H₃₈N₄O₄: 518; Found 519 (M+H)

EXAMPLE C1A

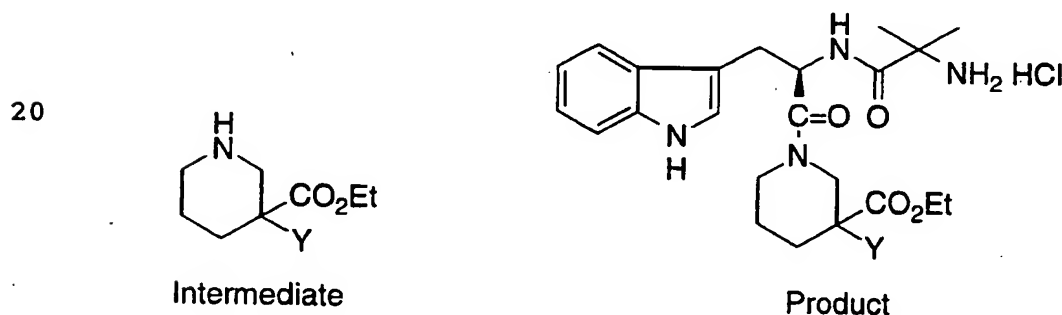
Prepared by the procedure described in Step C of Example C1 from 1 g of the d2 intermediates from the Step D of Example C1 in ethyl acetate (20 mL) by bubbling HCl at 0°C until saturated and then evaporated after 30 minutes to give the title compound (878 mg, 93%).
FAB-MS calc. for C₃₀H₃₈N₄O₄: 518; Found 519 (M+H)
¹H NMR (CD₃OD, 400MHz) compound exists in two rotamers in approximately a 5/3 ratio that slowly interconvert relative to the NMR time scale δ 7.60 (d, J = 7.9 Hz, 5/8 H), 7.55 (d, J = 7.9 Hz, 3/8 H), 7.34-6.93 (m, 9H), 5.36 (dd, J = 5.2Hz, 9.7 Hz, 3/8 H), 5.31 (dd, J = 6.7 Hz,

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8.8 Hz, 5/8 H), 4.23 (br. d, J = 13.7 Hz, 3/8 H), 4.10-4.00 (m, 6/8 H), 4.04-3.98 (m, 3/8 H), 3.96-3.82 (m, 10/8 H), 3.80 (br. d, J = 13.5 Hz, 5/8 H), 3.36 (br. d, J = 13.3 Hz, 5/8 H), 3.29-3.22, 3.17-3.10, (2m, 2H), 3.20 (br. d, J = 14.5 Hz, 3/8 H), 3.10-2.96 (m, 5/8 H), 2.90 (s, 6/8 H), 2.60 (d, J = 13.4 Hz, 5/8), 2.41 (d, J = 13.4 Hz, 5/8 H), 2.19-2.12, 1.82-1.70, 1.68-1.60, 1.50-1.40, 1.34-1.25, 1.05-0.95 (6m, 4 H), 1.55 (s, 9/8 H), 1.50 (s, 15/8 H), 1.09 (t, J = 7.1 Hz, 3 H).

The additional intermediates shown in Table CI were prepared according to the above established procedures as exemplified in Example C1 steps A through C. The final compounds were prepared according to Example C1 Steps D and E, and Example CIa using Intermediate 1.

TABLE CI: ADDITIONAL EXAMPLES

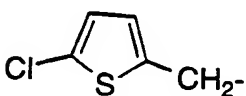
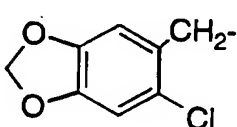
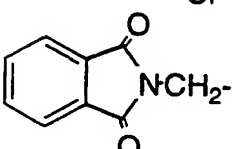


| entry | Y | Intermediate | Product | isomers ^a |
|-------|------|---|--|----------------------|
| | | MF FAB-MS (M+1) | MF FAB-MS (M+1) | |
| 1 | Me | C ₉ H ₁₇ NO ₂ 171 (M ⁺ , EI-MS) | C ₂₄ H ₃₄ N ₄ O ₄ 443 | d1 d2 |
| 2 | Et | C ₁₀ H ₁₉ NO ₂ 185 (M ⁺ , EI-MS) | C ₂₅ H ₃₆ N ₄ O ₄ 457 | d1 d2 |
| 3 | n-Pr | C ₁₁ H ₂₁ NO ₂ 199 (M ⁺ , EI-MS) | C ₂₆ H ₃₈ N ₄ O ₄ 471 | d1 d2 |

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| | | | | | |
|----|----|-------------------------------------|---|---|----|
| | 4 | allyl | C ₁₁ H ₁₉ NO ₂ | C ₂₆ H ₃₆ N ₄ O ₄ | d1 |
| | | | 198 | 469 | d2 |
| | 5 | n-Bu | C ₁₂ H ₂₃ NO ₂ | C ₂₇ H ₄₀ N ₄ O ₄ | d1 |
| | | | 213 (M ⁺ ,EI-MS) | 485 | d2 |
| 5 | 6 | -CH ₂ OEt | C ₁₁ H ₂₁ NO ₃ | C ₂₆ H ₃₈ N ₄ O ₅ | RS |
| | | | 216 | 487 | |
| | 7 | cyclohexane- methyl | C ₁₅ H ₂₇ NO ₂ | C ₃₀ H ₄₄ N ₄ O ₄ | d1 |
| | | | 254 | 525 | d2 |
| 10 | 8 | Ph(CH ₂) ₂ - | C ₁₆ H ₂₃ NO ₂ | C ₃₁ H ₄₀ N ₄ O ₄ | d1 |
| | | | 261 (M ⁺ ,EI-MS) | 533 | d2 |
| | 9 | Ph(CH ₂) ₃ - | C ₁₇ H ₂₅ NO ₂ | C ₃₂ H ₄₂ N ₄ O ₄ | d1 |
| | | | 275 (M ⁺ ,EI-MS) | 547 | d2 |
| | 10 | o-MeOBn- | C ₁₆ H ₂₃ NO ₃ | C ₃₁ H ₄₀ N ₄ O ₅ | d1 |
| | | | 278 | 549 | d2 |
| 15 | 11 | m-MeOBn- | C ₁₆ H ₂₃ NO ₃ | C ₃₁ H ₄₀ N ₄ O ₅ | d1 |
| | | | 278 | 549 | d2 |
| | 12 | p-MeOBn- | C ₁₆ H ₂₃ NO ₃ | C ₃₁ H ₄₀ N ₄ O ₅ | d1 |
| | | | 278 | 549 | d2 |
| 20 | 13 | o-Me-Bn- | C ₁₆ H ₂₃ NO ₂ | C ₃₁ H ₄₀ N ₄ O ₄ | d1 |
| | | | 262 | 533 | d2 |
| | 14 | m-Me-Bn- | C ₁₆ H ₂₃ NO ₂ | C ₃₁ H ₄₀ N ₄ O ₄ | d1 |
| | | | 262 | 533 | d2 |
| | 15 | p-Me-Bn- | C ₁₆ H ₂₃ NO ₂ | C ₃₁ H ₄₀ N ₄ O ₄ | d1 |
| | | | 262 | 533 | d2 |
| 25 | 16 | o-Cl-Bn- | C ₁₅ H ₂₀ NO ₂ Cl | C ₃₀ H ₃₇ N ₄ O ₄ Cl | d1 |
| | | | 282,284 (3:1) | 554,556 (3:1) | d2 |
| | 17 | m-Cl-Bn- | C ₁₅ H ₂₀ NO ₂ Cl | C ₃₀ H ₃₇ N ₄ O ₄ Cl | d1 |
| | | | 282,284 (3:1) | 554,556 (3:1) | d2 |
| 30 | 15 | p-Cl-Bn- | C ₁₅ H ₂₀ NO ₂ Cl | C ₃₀ H ₃₇ N ₄ O ₄ Cl | d1 |
| | | | 282,284 (3:1) | 554,556 (3:1) | d2 |
| | 16 | 2,6-di-Cl-Bn- | C ₁₅ H ₁₉ NO ₂ Cl ₂ | C ₃₀ H ₃₆ N ₄ O ₄ Cl ₂ | |
| | | | 316,318,320 | 587,589,591 | |
| | 17 | p-Br-Bn- | C ₁₅ H ₂₀ NO ₂ Br | C ₃₀ H ₃₇ N ₄ O ₄ Br | d1 |
| | | | 326,328 (1:1) | 597,599 (1:1) | d2 |

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| | | | | |
|----|---|---|---|----|
| 18 | m-Br-Bn- | C ₁₅ H ₂₀ NO ₂ Br | C ₃₀ H ₃₇ N ₄ O ₄ Br | d1 |
| | | 326,328 (1:1) | 597,599 (1:1) | d2 |
| 19 | o-nitro-Bn- | C ₁₅ H ₂₀ N ₂ O ₄ | C ₃₀ H ₃₇ N ₅ O ₆ | d1 |
| | | 293 | 564 | d2 |
| 20 | m-nitro-Bn- | C ₁₅ H ₂₀ N ₂ O ₄ | C ₃₀ H ₃₇ N ₅ O ₆ | d1 |
| | | 293 | 564 | d2 |
| 21 | p-nitro-Bn- | C ₁₅ H ₂₀ N ₂ O ₄ | C ₃₀ H ₃₇ N ₅ O ₆ | d1 |
| | | 293 | 564 | d2 |
| 22 | 1-naphthylmethyl | C ₁₉ H ₂₃ NO ₂ | C ₃₄ H ₄₀ N ₄ O ₄ | d1 |
| | | 298 | 569 | d2 |
| 23 |  | C ₁₃ H ₁₈ NO ₂ SCl | C ₂₈ H ₃₅ N ₄ O ₄ SCl | d1 |
| | | 288,290 (3:1) | 559,561(3:1) | d2 |
| 24 | BnO ₂ C- | C ₁₆ H ₂₁ NO ₄ | C ₃₁ H ₃₈ N ₄ O ₆ | RS |
| | | 292 | 563 | |
| 25 | EtO ₂ C- | C ₁₁ H ₁₉ NO ₄ | C ₂₆ H ₃₆ N ₄ O ₆ | RS |
| | | 230 | 501 | |
| 26 | p-Ph-Bn- | C ₂₁ H ₂₅ NO ₄ | C ₃₆ H ₄₂ N ₄ O ₄ | d1 |
| | | 324 | 595 | d2 |
| 27 |  | C ₁₆ H ₂₀ NO ₄ Cl | C ₃₁ H ₃₇ N ₄ O ₆ Cl | d1 |
| | | 326, 328(3:1) | 597, 599(3:1) | d2 |
| 28 |  | C ₁₇ H ₂₀ N ₂ O ₄ | C ₃₂ H ₃₇ N ₅ O ₆ | d1 |
| | | 317 | 588 | d2 |

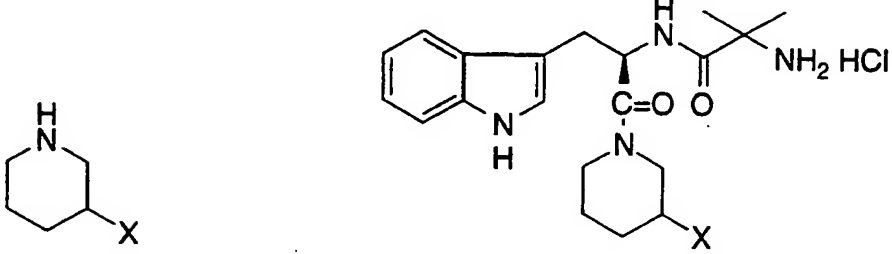
^a: In this and in subsequent tables for isomer designation: R or S means the stereochemistry at the carbon atom to which X and Y are attached, RS means it is a mixture of the two isomers at this center; d1 or d2 means the two diastereomers were separated and are as defined in Example C1 step D.

The additional examples shown in Table C1a were prepared according to Example C1 Steps D and E, using Intermediate 1 and commercially available intermediates.

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TABLE CIa: ADDITIONAL EXAMPLES

5



10

| Intermediate | | Product | |
|--------------|---------------------|--|--------|
| entry | X | MF FAB-MS (M+1) | isomer |
| 1 | -OH | C ₂₀ H ₂₈ N ₄ O ₃ 373 | RS |
| 2 | -CH ₂ OH | C ₂₁ H ₃₀ N ₄ O ₃ 387 | RS |
| 3 | -CO ₂ Et | C ₂₃ H ₃₂ N ₄ O ₄ 429 | RS |
| 4 | CO ₂ Bn | C ₂₈ H ₃₄ N ₄ O ₄ 491 | RS |
| 5 | CONMe ₂ | C ₂₃ H ₃₃ N ₅ O ₃ 428 | RS |

15

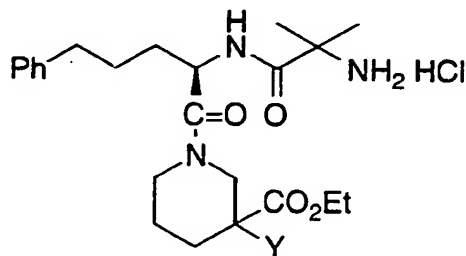
20

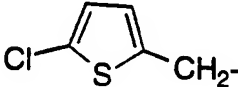
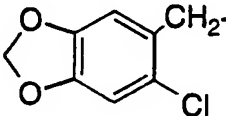
The additional Products shown in Table CIb were prepared according to Example C1 Steps D and E, using Intermediate 3 and some of the intermediates shown in Table C1.

25

30

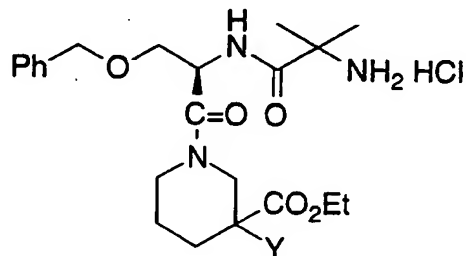
- 264 -

TABLE CIb: ADDITIONAL EXAMPLES

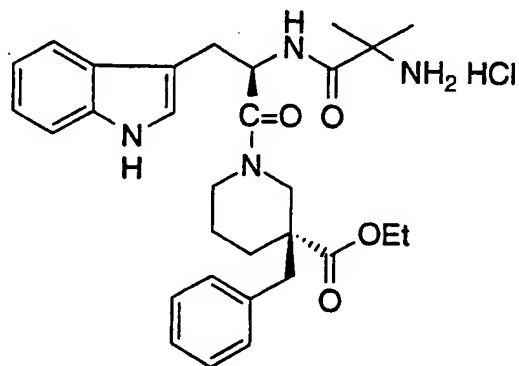
| entry | Y | Product | |
|--------------|---|--------------------------------|----------|
| | | MF | isomer |
| FAB-MS (M+1) | | | |
| 1 | Bn | C30H41N3O4 508 | R |
| 2 | Bn | C30H41N3O4 508 | S |
| 3 | Ph(CH2)2 | C31H43N3O4 522 | d1 d2 |
| 4 | Ph(CH2)3 | C32H45N3O4 536 | d1 d2 |
| 5 | 1-naphthylmethyl | C34H43N3O4 558 | RS |
| 6 |  | C28H38N3O4SCl 548,550 (3:1) | RS |
| 7 | p-Ph-Bn- | C36H45N3O4 584 | RS |
| 8 | BnO2C- | C31H41N3O6 552 | RS |
| 9 |  | C31H40N3O6Cl 586,588 (3:1) | d1 d2 |

The additional products shown in Table CIc were prepared according to Example C1 Steps D and E, using Intermediate 2 and some of the intermediates shown in Table CI.

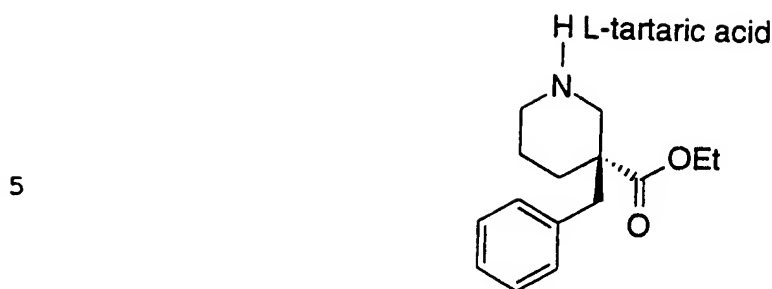
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TABLE C1c: ADDITIONAL EXAMPLES

| entry | Y | MF | isomer |
|--------------|----------|-------------------|----------|
| FAB-MS (M+1) | | | |
| 1 | Bn | C29H39N3O5 510 | R |
| 2 | Bn | C29H39N3O5 510 | S |
| 3 | Et | C24H37N3O5 448 | RS |
| 4 | Ph(CH2)2 | C30H41N3O5 524 | d1 d2 |
| 5 | Ph(CH2)3 | C31H43N3O5 538 | d1 d2 |
| 6 | H | C22H33N3O5 420 | RS |

EXAMPLE C2Step A:

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10 The intermediate from Example C1, Step C (50.8 g) was dissolved in dichloromethane and it was washed with 3N NaOH. The aqueous layer was extracted with dichloromethane and the combined solution was dried (MgSO₄) and evaporated to give the free amine as an oil. The ethyl 3-benzyl nipecotate and D-tartaric acid (31 g) were dissolved in 880 mL of water/acetone (1:4) solution with heating. The solution was left in the refrigerator overnight and the crystals which were
15 formed were filtered off. Recrystallization in 470 mL of water/acetone (1:4) at room temperature gave the ethyl 3-(R)-benzyl nipecotate D-tartaric acid salt (21 g).

20 The structure of this compound was determined by X-Ray crystallographic analysis. With the configuration of D-tartaric acid known to be S,S, the configuration of the chiral site in this ethyl 3-benzyl nipecotate salt was determined to be R.

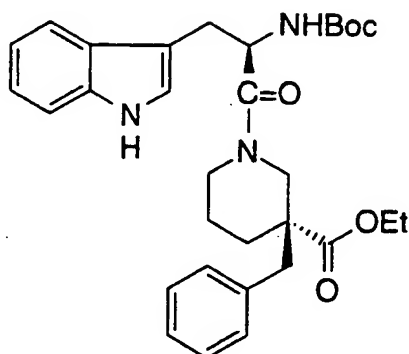
25 The combined mother liquor was evaporated and to it was added 3N NaOH and dichloromethane, the mixture was stirred for 30 minutes and the organic layer was separated. The aqueous was extracted twice with dichloromethane and the combined organic extracts were dried over MgSO₄ and evaporated to give 24.4 g of the S-isomer enriched compound. It was crystallized with L-tartaric acid (14.8 g) in 400 mL of water/acetone (1:4) at room temperature to give ethyl 3 (S)-benzyl nipecotate L-tartaric acid salt (27.3 g).

30 ¹H NMR (CD₃OD, 400MHz) δ 7.31-7.22 (m, 3 H), 7.12-7.09 (m, 2 H), 4.40 (s, 2 H, from tartaric acid), 4.30-4.10 (m, 2 H), 3.49 (br. d, J = 13 Hz, 1 H), 3.06 (d, J = 13.6 Hz, 1 H), 2.98 (d, J = 13 Hz, 1 H), 2.92 (dt, J = 3.3 Hz, 13 Hz, 1 H), 2.82 (d, J = 13.6 Hz, 1 H), 2.30 (d, J = 12.4 Hz, 1

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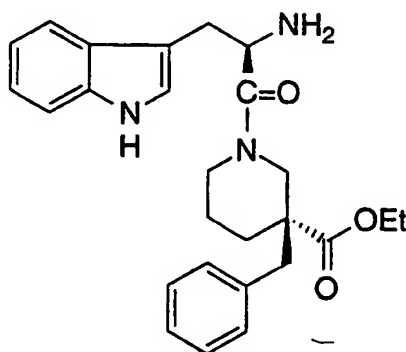
H), 1.88 (td, $J = 3$ Hz, 14.5 Hz, 1 H), 1.69 (dt, $J = 3$ Hz, 13 Hz, 1 H), 1.63-1.51 (m, 1 H), 1.25b (q, $J = 7.1$ Hz, 3 H).

Step B:



Ethyl 3 (S)-benzyl nipecotate L-tartaric acid salt (39.74 g) was suspended in 70 mL of 3N NaOH and 70 mL of water, followed by extraction with dichloromethane. The extracts were combined, dried, and evaporated to give a thick oil. To a stirred solution of the oil, N-t-Boc D-TrpOH (30.43 g) and HOBt (13.5 g) in dichloromethane (200 mL) at 0°C, was added EDC (23 g) in several portions. The mixture was stirred overnight and it was poured into water and 3 N HCl and was extracted with dichloromethane. The organic layer was washed with brine, saturated sodium bicarbonate, dried over MgSO₄ and evaporated to give a crude product (67.7 g), which was used without further purification. FAB-MS calc. for C₃₁H₃₉N₃O₅: 533; Found 534 (M+H)

Step C:

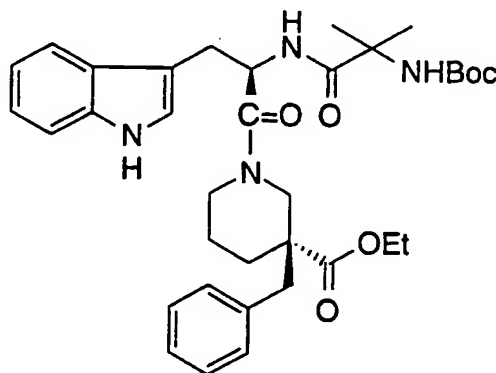


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To a solution of the intermediate from the previous step (67.7 g crude) in ethyl acetate (100 mL) at 0°C, was bubbled HCl gas until it was saturated. The reaction mixture was stirred at 0°C for 30 minutes and was evaporated to remove excess HCl and ethyl acetate. The residue was suspended in dichloromethane and was washed with a mixture of 3 N NaOH (70 mL) and water (100 mL). The organic layer was dried (MgSO₄), evaporated to a small volume and used in next step without further purification.

FAB-MS calc. for C₂₆H₃₁N₃O₃: 433; Found 434 (M+H)

Step D:

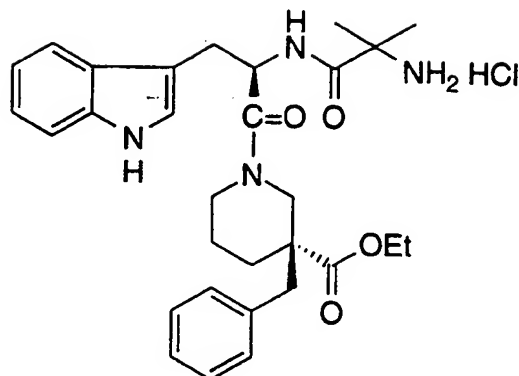


A solution containing the intermediate obtained in the last step, N-Boc- α -Me-AlaOH (20.3 g), and DMAP (200 mg) in dichloromethane (100 mL) was stirred at room temperature and to it was added EDC (24 g) in several portions. The reaction mixture was stirred for 3 hours and was worked up by diluting it with dichloromethane and washing with 3 N HCl, brine, and saturated sodium bicarbonate solution. The organic layer was dried over MgSO₄, and evaporated to give a thick oil. This oil was passed through a pad of silica gel, eluting with 60% ethyl acetate in hexane to remove some very polar impurities, to give the desired compound (54.2 g)

FAB-MS calc. for C₃₅H₄₆N₄O₆: 618; Found 619 (M+H)

Step F:

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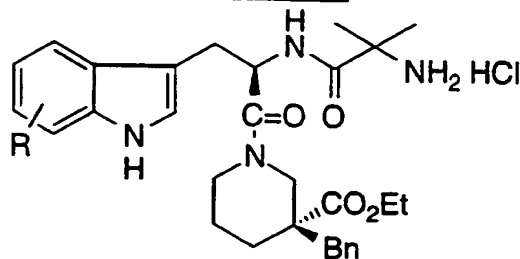


To a solution of the intermediate from the previous step (54.2 g) in ethyl acetate (100 mL) at 0°C, was bubbled HCl gas until it was saturated. The reaction mixture was stirred at 0°C for 15 minutes and was evaporated to remove excess HCl and ethyl acetate. The residue was first dissolved in dichloromethane (100 mL) and then ethyl acetate (300 mL) was added. The mixture was stirred overnight and the solid was collected by filtration to give the title compound (34 g). Further evaporation of the mother liquor to a small volume gave the second crop of product (10.1 g).

MS and NMR identical with Example C1A.

The additional products shown in Table CII were prepared according to Example C2, Steps B through F, using the readily available Boc protected amino acids instead of N-t-Boc-D-TrpOH.

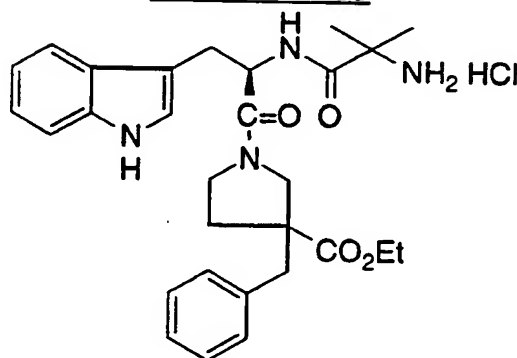
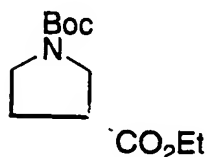
TABLE CII



Product

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| entry | R | MF |
|-------|-------|--------------------|
| | | FAB-MS (M+1) |
| 1 | 4-F | C30H37N4O4F 537 |
| 2 | 5-F | C30H37N4O4F 537 |
| 3 | 6-F | C30H37N4O4F 537 |
| 4 | 1-Me | C31H40N4O4 533 |
| 5 | 5-MeO | C31H40N4O5 549 |
| 6 | 5-HO | C30H38N4O5 535 |
| 7 | 6-MeO | C31H40N4O5 549 |

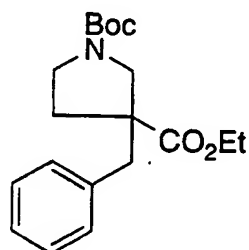
EXAMPLE C3Step A:

To a stirred solution of ethyl 3-pyrrolidinecarboxylate hydrochloride (J. Chem. Soc., 24, 1618-1619; 10 g, 69.8 mmol), triethylamine (7.75 mL) and DMAP (857 mg) in dichloromethane (40 mL), was slowly added di-t-butyl dicarboxylate (18.3 g, 83.7 mmol) and

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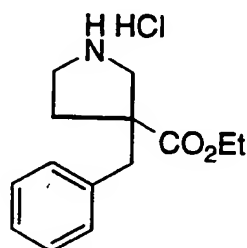
the resulting mixture was stirred at room temperature for three days. The mixture was then concentrated, washed with 3 N HCl and dried and evaporated to give the intermediate.

5 Step B:



Prepared by the procedure described in Example C1, Step B from the intermediate obtained from previous step (500 mg, 2.05 mmol), KHMDS (512 mg, 2.57 mmol) and benzyl bromide (371 mg, 2.16 mmol).
15 Purification by silica gel flash column eluting with 5-20% ethyl acetate in hexane provided the title compound (385 mg, 56%).

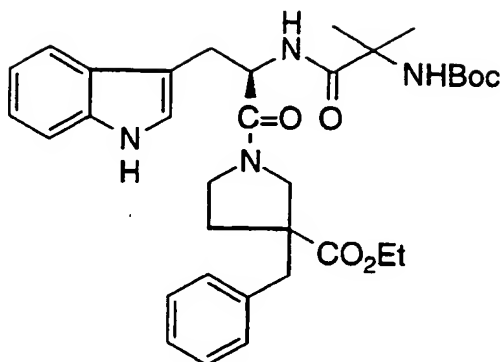
Step C:



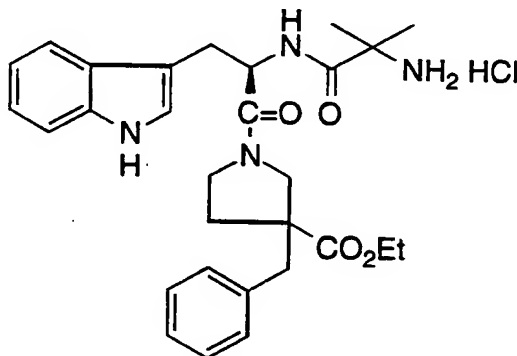
25 Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (385 mg, 1.16 mmol) in ethyl acetate (5 mL) and HCl gas at 0°C for 15 minutes (306 mg, 98%).

30

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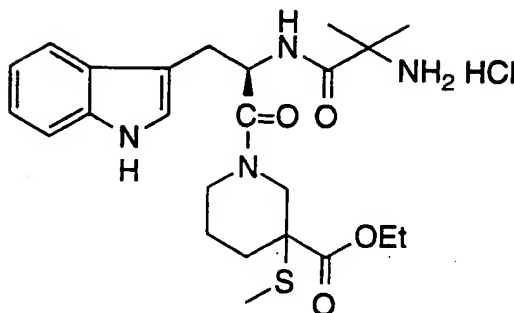
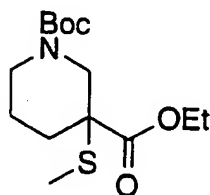
Step D:

Prepared by the procedure described in Example C1, Step D from the intermediate prepared in the previous step (138 mg, 0.514 mmol), intermediate 1 (200 mg, 0.514 mmol), HOBT (1 eq.), N-methyl morpholine (1 eq.), and EDC (2 eq.). Purification by MPLC, eluting with 60% ethyl acetate in hexane gave the product (250 mg, 80%)
FAB-MS calc. for C₃₄H₄₄N₄O₆: 604; Found 605 (M+H).

Step E:

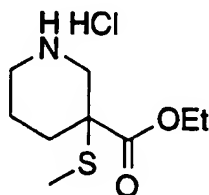
Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (250 mg, 0.036 mmol) in ethyl acetate (3 mL) and HCl gas at 0°C for 10 minutes.
FAB-MS calc. for C₂₉H₃₆N₄O₄: 504; Found 505 (M+H).

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EXAMPLE C4Step A:

To a stirred solution of ethyl N-t-Boc nipecotate (4 g, 15.7 mmol) in THF (100 mL) at -78°C under argon was added LHMDs (1 M, 32 mL, 32 mmol) over a 10 minute period. The solution was allowed to stir an additional 30 minutes at -78°C ; then methyl disulfide (1.92 g, 20.37 mmol) was added slowly to the solution. The reaction mixture was stirred overnight and allowed to warm to room temperature. The material was concentrated, then diluted with water, and extracted using ethyl acetate (2 x 200 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by silica gel flash column chromatography eluting with 20% ethyl acetate in hexane provided the title compound.

FAB-MS calc. for $\text{C}_{14}\text{H}_{25}\text{NO}_4\text{S}$: 271; Found 272 (M+H)

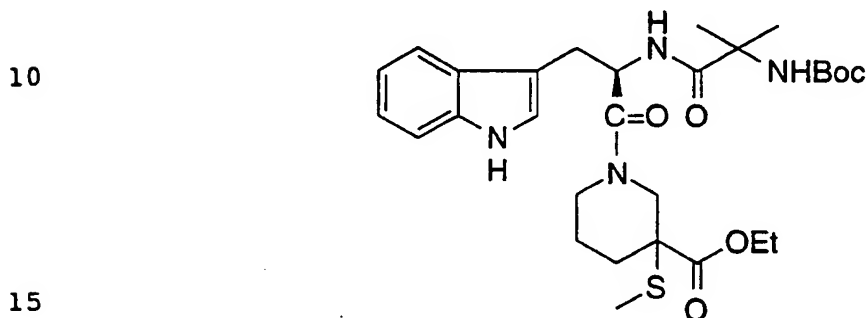
Step B:

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Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (1 g, 3.3 mmol) in ethyl acetate (25 mL) and HCl gas at 0°C for 35 minutes to yield the product (783 mg, 99%).

5 FAB-MS calc. for $C_9H_{17}NO_2S$: 171; Found 271 (M+H)

Step C:

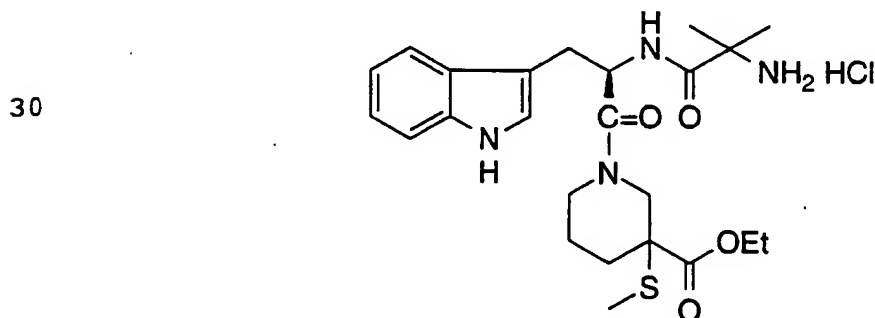


Prepared by the procedure described in Example C1, Step D from the intermediate prepared in the previous step (123 mg, 0.514 mmol), Intermediate 1 (1 eq.), HOBT (1 eq.), NMM (1 eq.), and EDC (197 mg, 1.028 mmol). Purification by MPLC provided diastereomers. The compound which came out first from the column was designated as d1 (109 mg, 37%); and the compound which came out of the column second was designated as d2 (88 mg, 30%), d1 FAB-MS calc. for $C_{29}H_{42}N_4O_6S$: 574; Found 575 (M+H) d2 FAB-MS calc. for $C_{29}H_{42}N_4O_6S$: 574; Found 575 (M+H)

20

25

Step D:



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Prepared by the procedure described in Example C1, Step C from the intermediates d1(80 mg) and d2 (80 mg) separately from the previous step in ethyl acetate (5 mL each) and HCl gas at 0°C for 20 minutes.

5 d1: (71 mg, 99%)

d2: (70 mg, 98%)

d1 ¹H NMR (CD₃OD, 400MHz): The compound exists in two rotamers in approximately a 1:1 ratio. δ 7.71 (d, J = 7.2 Hz, 1/2 H), 7.56 (d, J = 7.2 Hz, 1/2 H), 7.38 (d, J = 8.0 Hz, 1/2 H), 7.33 (d, J = 7.5 Hz, 1/2 H),
10 7.14-7.01 (m, 3 H), 5.44 (dd, J = 6 Hz, 8 Hz, 1/2 H), 4.30-4.10 (m, 5/2 H), 3.92 (d, J = 13.3 Hz, 1/2 H), 3.81 (d, J = 13.3 Hz, 1/2 H), 3.67 (d, J = 13.3 Hz, 1/2 H), 3.48-3.40 (m, 1/2 H), 3.28-3.09 (m, 7/2 H), 2.55 (dt, 1/2 H), 2.26-2.20 (br. d, 1/2 H), 2.05 (s, 3 H), 1.80-1.70 (m, 1/2 H), 1.67, 1.59, 1.55, 1.43 (4s, 6 H), 1.27 (t, J = 7.0 Hz, 3/2 H), 1.19 (t, J = 7.0 Hz, 3/2 H),
15 0.90-0.85 (m, 1/2 H).

d2 ¹H NMR (CD₃OD, 400MHz): The compound exists in two rotamers in approximately a 1:1 ratio. δ 7.77 (d, J = 7.5 Hz, 1/2 H), 7.56 (d, J = 7.9 Hz, 1/2 H), 7.35-7.30 (m, 1 H), 7.13-6.98 (m, 3 H), 5.53 (dd, J = 5.5 Hz, 8 Hz, 1/2 H), 5.24 (app. t, J = 7 Hz, 1/2 H), 4.30 (br. d, J = 14 Hz, 1/2 H), 4.20-4.10 (m, 2 H), 3.90-3.85 (m, 1/2 H), 3.86 (d, J = 13.2 Hz, 1/2 H), 3.70 (d, J = 13.7 Hz, 1/2 H), 3.35-3.10 (m, 4 H), 2.30-2.20 (m, 1/2 H), 2.12, 2.04 (2s, 3 H), 2.04-2.00 (m, 1/2 H), 1.80-1.70 (m, 3/2 H), 1.54, 1.50, 1.43, 1.26 (4s, 6 H), 1.23 (t, J = 6.7 Hz, 3 H), 0.90-0.84 (m, 1/2 H).

25 d1 FAB-MS calc. for C₂₄H₃₄N₄O₄S: 474; Found 475 (M+H)

d2 FAB-MS calc. for C₂₄H₃₄N₄O₄S: 474; Found 475 (M+H)

The additional intermediates shown in Table CIII were prepared according to the above established procedure as exemplified in Example C4 steps A and B. The final compounds were prepared according to Example C4 Steps C and D, using Intermediate 1.

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TABLE CIII

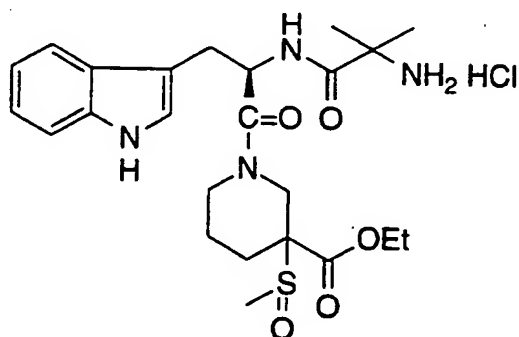
Intermediate

Product

| entry | Y | Intermediate MF FAB-MS (M+1) | Product MF FAB-MS (M+1) | isomer |
|-------|----------------|--|---|----------|
| 1 | PhS- | C ₁₄ H ₁₉ NO ₂ S 266 | C ₂₉ H ₃₆ N ₄ O ₄ S 537 | d1 d2 |
| 2 | BnS- | C ₁₅ H ₂₁ NO ₂ S 280 | C ₃₀ H ₃₈ N ₄ O ₄ S 551 | d1 d2 |
| 3 | 2-pyridylthio- | C ₁₃ H ₁₈ N ₂ O ₂ S 267 | C ₂₈ H ₃₅ N ₅ O ₄ S 538 | RS |
| 4 | | | C ₂₇ H ₃₅ N ₅ O ₄ S ₂ 558 | RS |

EXAMPLE C5

25

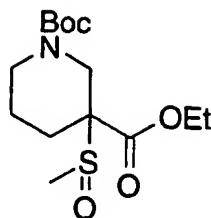


30

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Step A:

5



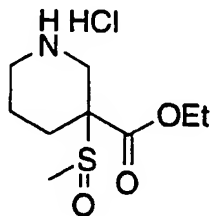
To a stirred solution of NaIO₄ (316.5 mg, 1.48 mmol) in water (5 mL) and ethanol (5 mL) was added the intermediate from Example C4, Step A (300 mg, 0.99 mmol). The mixture was stirred for 5 hours at room temperature, then concentrated to remove ethanol. The material was then extracted with ethyl acetate (2 x 10 mL). The organic layer was dried over magnesium sulfate and concentrated to give the title compound (286 mg, 90.5%).

FAB-MS calc. for C₁₄H₂₅NO₅S: 319; Found 320 (M+H)

15

Step B:

20



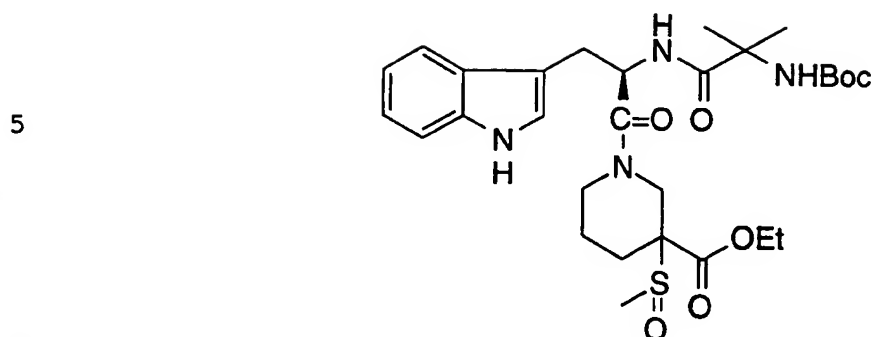
Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (230 g, 0.72 mmol) in ethyl acetate (10 mL) and HCl gas at 0°C for 25 minutes (197 mg, 100%).

FAB-MS calc. for C₉H₁₇NO₃S: 219; Found 220 (M+H)

25

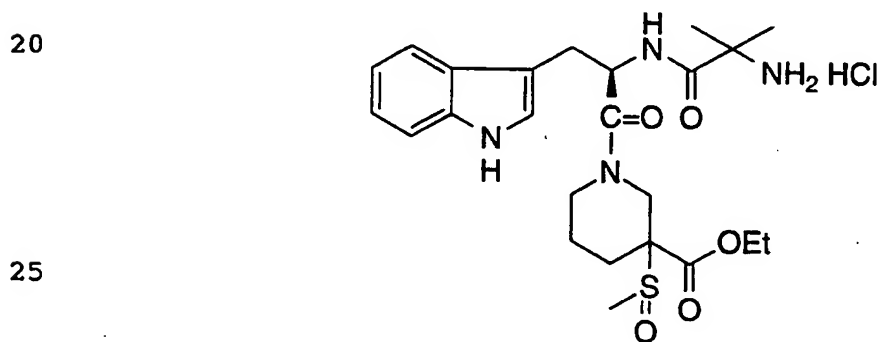
30

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Step C:

Prepared by the procedure described in Example C1, Step D from the intermediate prepared in the previous step (140 mg, 0.547 mmol), Intermediate 1 (1 eq.), HOBT (1 eq.), N-methyl morpholine (1 eq.), and EDC (210 mg, 1.094 mmol). Purification by MPLC provided a

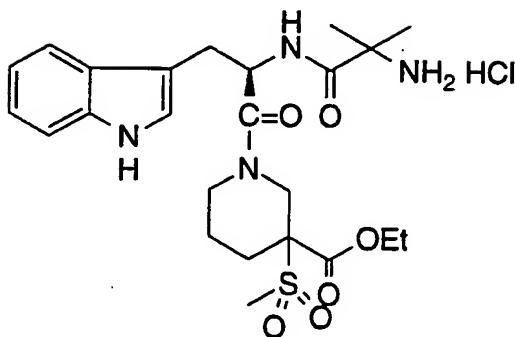
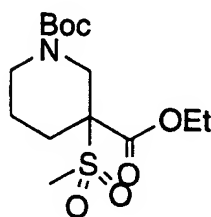
15 diastereomeric mixture of compounds (177 mg, 55%).
FAB-MS calc. for $C_{29}H_{42}N_4O_7S$: 590; Found 591 (M+H)

Step D:

Prepared by the procedure described in Example C1, Step C

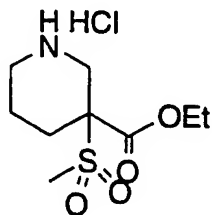
30 from the intermediate from the previous step (150 mg, 0.254 mmol) in ethyl acetate (10 mL) and HCl gas at 0°C for 20 minutes (118 mg, 90%).
FAB-MS calc. for $C_{24}H_{34}N_4O_5S$: 490; Found 491 (M+H)

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EXAMPLE C6Step A:

To a stirred solution of Oxone (910 mg, 1.48 mmol) in water (5 mL) and methanol (5 mL) was added the intermediate from Example C4, Step A (300 mg, 0.99 mmol). The mixture was stirred for 4 hours at room temperature, then concentrated to remove methanol. The residue was then extracted with ethyl acetate (2 x 10 mL). The organic layer was dried over magnesium sulfate and concentrated to give the title compound (321 mg, 97%).

FAB-MS calc. for C₁₄H₂₅NO₆S: 335; Found 336 (M+H) [Found 236 (M- t-Boc)]

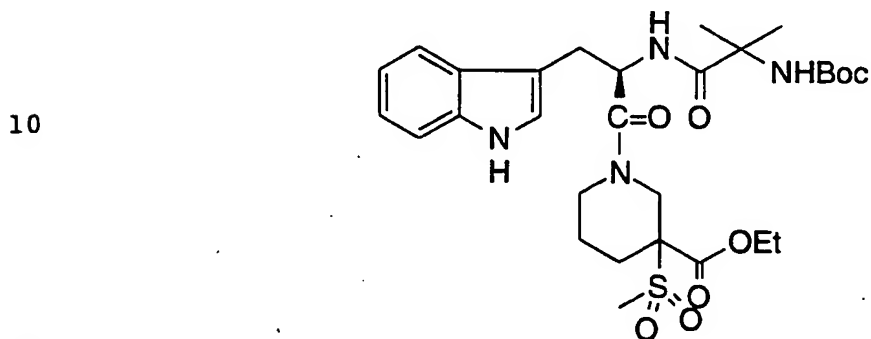
Step B:

- 280 -

Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (221 mg, 0.66 mmol) in ethyl acetate (10 mL) and HCl gas at 0°C for 25 minutes (192 mg, 99%). FAB-MS calc. for C₉H₁₇NO₄S: 235; Found 236 (M+H)

5

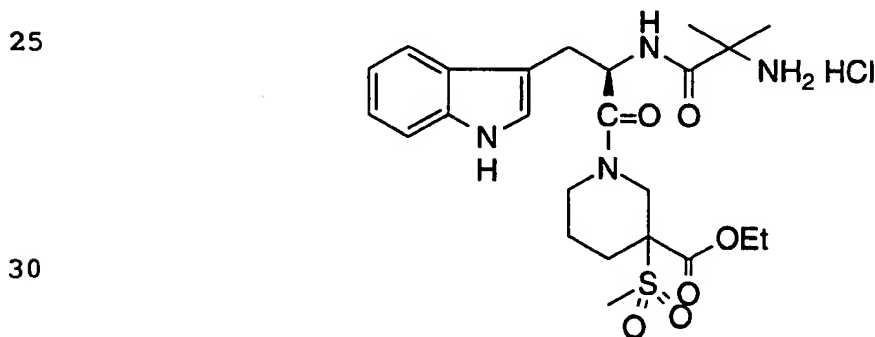
Step C:



15

Prepared by the procedure described in Example C1, Step D from the intermediate prepared in the previous step (140 mg, 0.515 mmol), Intermediate 1 (1 eq.), HOBT (1 eq.), N-methyl morpholine (1 eq.), and EDC (197 mg, 1.03 mmol.). Purification by MPLC provided a
20 diastereomeric mixture of compounds (251 mg, 80%).
FAB-MS calc. for C₂₉H₄₂N₄O₈S: 606; Found 607 (M+H)

Step D:



30

Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (210 mg, 0.317 mmol) in

- 281 -

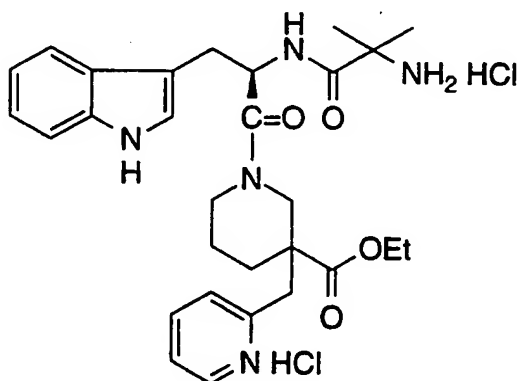
ethyl acetate (10 mL) and HCl gas at 0°C for 30 minutes (193 mg, 98.5%) FAB-MS calc. for C₂₄H₃₄N₄O₈S: 506; Found 507 (M+H)

EXAMPLE C7

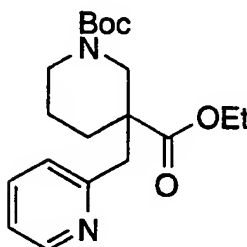
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Step A:

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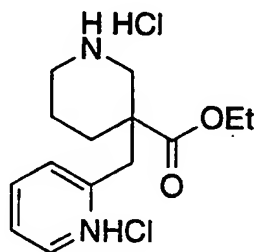
25

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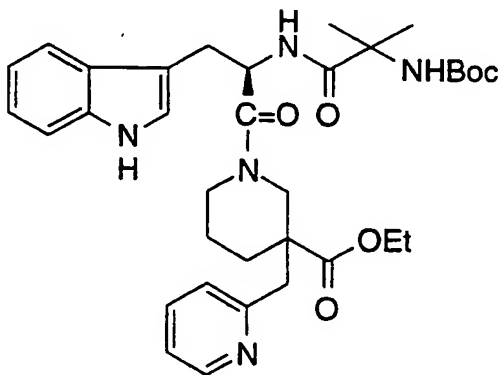
To a stirred solution of ethyl N-t-Boc nipecotate (50 g, 0.196 mol) in THF (600 mL) at -78°C under argon was added KHMDS (0.5 M in toluene, 298 mL, 0.298 mol) over a 30 minute period. The solution was allowed to stir an additional 30 minutes at -78°C. Meanwhile, a suspension of 2-picolyl chloride hydrochloride (25 g) in dichloromethane was washed with a mixture of 3 N NaOH and brine to remove the hydrochloride. The organic layer was dried over MgSO₄ and evaporated to yield a brown oil and it was added slowly to the solution at -78°C. The reaction mixture was stirred overnight and allowed to warm to room temperature. The material was concentrated, then diluted with water, and extracted using ethyl acetate. The organic layer was dried over

- 282 -

anhydrous magnesium sulfate, filtered, and concentrated. Purification by silica gel flash column chromatography eluting with a solvent gradient of 20-80% ethyl acetate in hexane provided the title compound. (54.8 g, 80%). ^1H NMR (CD_3OD , 400MHz) δ 8.45 (dd, $J = 1.5$ Hz, 5 Hz, 1 H), 7.52 (app dt, $J = 2$ Hz, 8 Hz, 1 H), 7.07 (dd, $J = 5$ Hz, 6.6 Hz, 1 H), 7.05 (d, $J = 8$ Hz, 1 H), 4.09-4.04 (br. m, 2 H), 3.92 (br. d, 1 H), 3.46 (br. m, 1 H), 3.30-3.10 (br. m, 1 H), 3.06 (d, $J = 13.7$ Hz, 1 H), 2.95 (d, $J = 13.7$ Hz, 1 H), 2.01-1.91 (br. m, 1 H), 1.63-1.50 (br. m, 3 H), 1.36 (v. br. s, 9 H), 1.13 (t, 7.1 Hz, 3 H). FAB-MS calc. for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_4$: 348; Found 349 ($\text{M}+\text{H}$)

Step B:

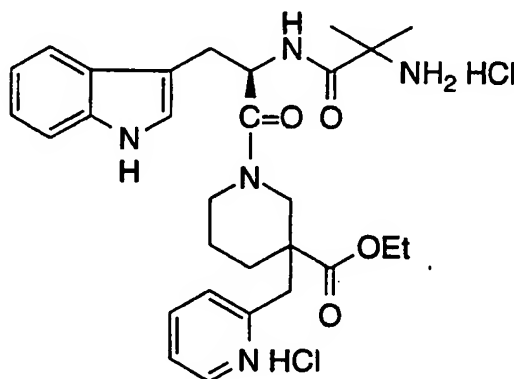
Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (6.36g, 18.2 mmol) in ethyl acetate (100 mL) and HCl at 0°C for 45 minutes (6.10g, 100%). FAB-MS calc. for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_2$: 248; Found 249 ($\text{M}+\text{H}$)

Step C:

- 283 -

Prepared by the procedure described in Example C1, Step D from the compound prepared in the previous step (500 mg, 1.556 mmol), Intermediate 1(1 eq.), HOBT (1 eq.), N-methyl morpholine (2 eq.), and EDC (597 mg, 3.11 mmol). Purification by MPLC eluting with ethyl acetate provided the title compound (883 mg, 91.5%). FAB-MS calc. for C₃₄H₄₅N₅O₆: 619; Found 620 (M+H)

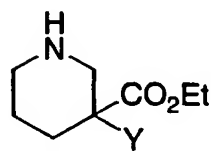
Step D:



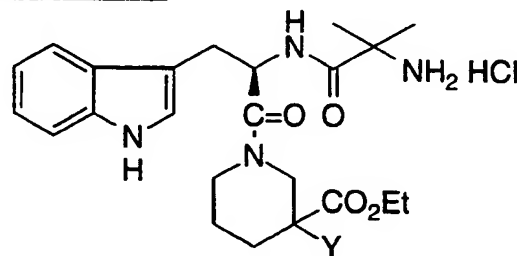
Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (250 mg, 0.404 mmol) in ethyl acetate (25 mL) and HCl gas at 0°C for 25 minutes (204 mg, 85%) FAB-MS calc. for C₂₉H₃₇N₅O₄: 519; Found 520 (M+H)

The additional intermediates shown in Table CIV were prepared according to the above established procedure as exemplified in Example C7 step A and B. The final compounds were prepared according to Example C7 Steps C and D, using Intermediate 1.

TABLE CIV

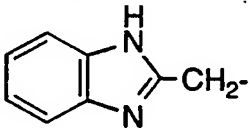
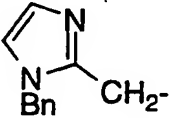
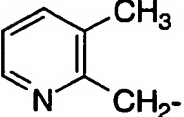


Intermediate



Product

- 284 -

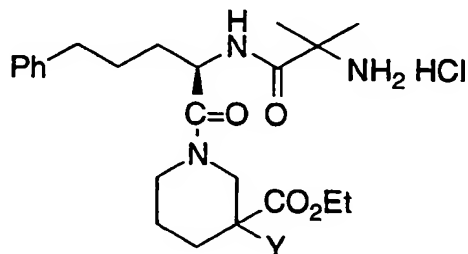
| entry | Y | Intermediate | Product | isomer |
|-------|---|---|--|----------|
| | | MF FAB-MS (M+1) | MF FAB-MS (M+1) | |
| 5 | 1 | 3-picolyl C ₁₄ H ₂₀ N ₂ O ₂ 249 | C ₂₉ H ₃₇ N ₅ O ₄ 520 | RS |
| | 2 | 4-picolyl C ₁₄ H ₂₀ N ₂ O ₂ 249 | C ₂₉ H ₃₇ N ₅ O ₄ 520 | RS |
| | 3 | 2-quinoline- methyl C ₁₈ H ₂₂ N ₂ O ₂ 298 | C ₃₃ H ₃₉ N ₅ O ₄ 569 | RS |
| 10 | 4 |  C ₁₆ H ₂₁ N ₃ O ₂ 288 | C ₃₁ H ₃₈ N ₆ O ₄ 559 | d1 d2 |
| | 5 |  C ₁₉ H ₂₅ N ₃ O ₂ 328 | C ₃₄ H ₄₂ N ₆ O ₄ 599 | RS |
| 15 | 6 |  C ₁₅ H ₂₂ N ₂ O ₂ 263 | C ₃₀ H ₃₉ N ₅ O ₄ 534 | RS |

The additional compounds shown in Table CIVa were prepared according to Example C7 Steps C and D, using some of the intermediates shown in Table CIV and Intermediate 3 instead of Intermediate 1.

TABLE CIVa: ADDITIONAL EXAMPLES

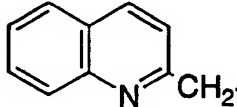
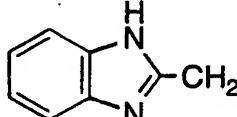
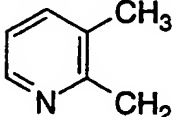
25

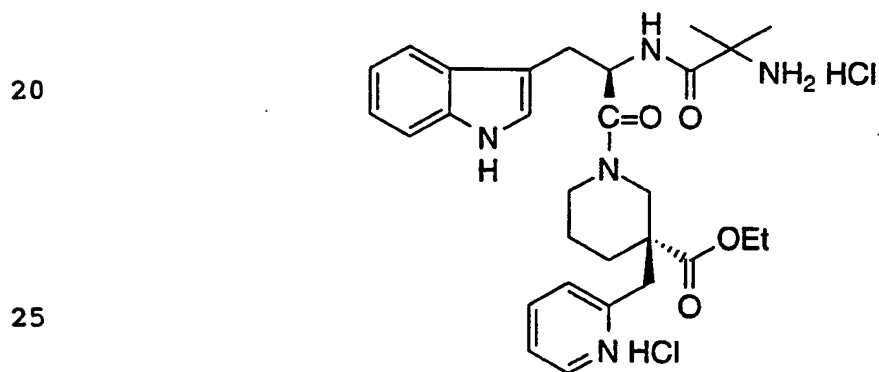
30



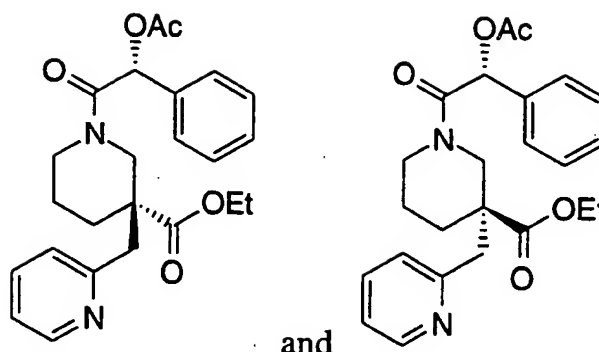
| entry | Y | MF FAB-MS (M+1) | isomer |
|-------|---|--------------------|--------|
|-------|---|--------------------|--------|

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| | | | | |
|----|---|---|--|----------|
| | 1 | 2-picolyl | C ₂₉ H ₄₀ N ₄ O ₄ 509 | d1 d2 |
| | 2 | 3-picolyl | C ₂₉ H ₄₀ N ₄ O ₄ 509 | d1 d2 |
| 5 | 3 | 4-picolyl | C ₂₉ H ₄₀ N ₄ O ₄ 509 | d1 d2 |
| | 4 |  | C ₃₃ H ₄₂ N ₄ O ₄ 559 | RS |
| 10 | 5 |  | C ₃₁ H ₄₁ N ₅ O ₄ 548 | d1 d2 |
| | 6 |  | C ₃₀ H ₄₂ N ₄ O ₄ 523,545(M+Na) | d1 d2 |
| 15 | | | | |

EXAMPLE C8

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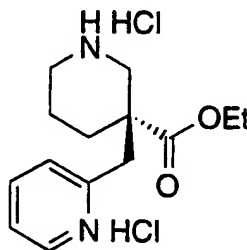
Step A:

Prepared by the procedure described in Example C1, Step D from the intermediate (6g, 18.67 mmol) prepared in Example C7, Step B, and using (R)-(-)-O-acetyl mandelic acid (1 eq.), HOBT (1 eq.), N-methyl morpholine (2 eq.), and EDC (7.16 g, 37.34 mmol). Purification by MPLC eluting with 80% ethyl acetate in hexane provided two enantiomerically pure compounds. The isomer which came out of the column first was designated as d1 (3.92 g, 99%) and the isomer which came out of the column second as d2 (3.69 g, 93%)

15

FAB-MS calc. for C₂₄H₂₈N₂O₅ Found 425. The structure of intermediate d1 was determined by x-ray crystallography. Given the absolute stereochemistry of (R) -O- acetylmandelic acid, the stereochemistry at the piperidine 3-position was assigned (S)- in d1.

20

Step B:

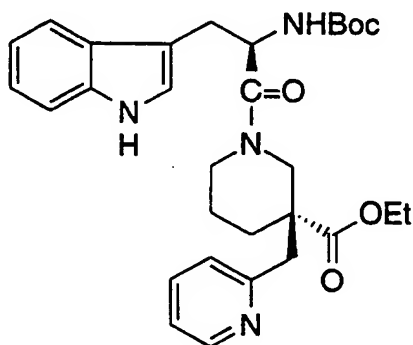
The intermediate d1 from the previous step (2.91g, 6.86 mmol) in ethanol (30 mL) and concentrated HCl (25 mL) was refluxed for five hours. The reaction mixture was evaporated *in vacuo* and the

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residue was purified by silica gel flash column chromatography eluting with a solvent gradient of 1:10:90 to 2:20:80 ammonium

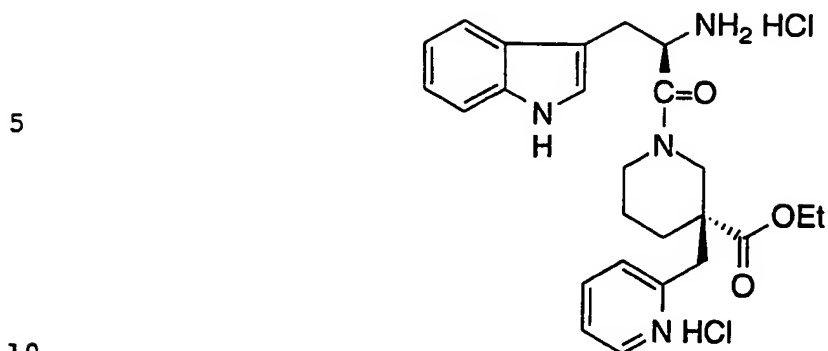
hydroxide:methanol:chloroform to provide the compound (d1, 1.52g, 70%). ¹H NMR (CD₃OD, 400MHz) δ 8.84 (app. d, J = 6 Hz, 1 H), 8.60 (app. dt, J = 1.5 Hz, 8 Hz, 1 H), 8.04 (t, J = 6 Hz, 1 H), 7.94 (d, J = 8 Hz, 1 H), 4.34-4.27 (m, 1 H), 4.23-4.17 (m, 1 H), 3.75 (d, J = 13 Hz, 1 H), 3.46 (d, J = 13.3 Hz, 1 H), 3.40 (d, J = 13.3 Hz, 1 H), 3.31-3.29 (m, 2 H), 3.20 (d, J = 13 Hz, 1 H), 3.03 (app dt, J = 3.1 Hz, 12.8 Hz, 1 H), 2.24 (br. d, 1 H), 2.00-1.93 (m, 1 H), 1.88 (dd, J = 3.7 Hz, 13.5 Hz, 1 H), 1.63-1.60 (m, 1 H), 1.23 (t, 7.1 Hz, 3 H). FAB-MS calc. for C₁₄H₂₀N₂O₂: 248; Found 249 (M+H)

Step C:



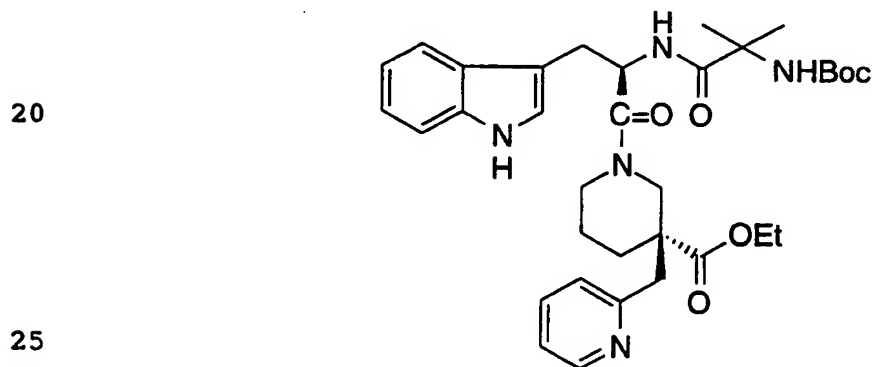
Prepared by the procedure described in Example C1, Step D from the intermediate prepared in Step B of this example (d1, 1.50g, 4.67 mmol), N-t-Boc-D-Trp (1 eq.), HOBT (1 eq.), and EDC (1.53g, 8.00 mmol). Purification by MPLC eluting with ethyl acetate provided the title compound (1.764 g, 71%). FAB-MS calc. for C₃₀H₃₈N₄O₅: 534; Found 535 (M+H)

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Step D:

Prepared by the procedure described in Example C3, Step C from the intermediate from the previous step (1.658 g, 3.11 mmol) in ethyl acetate (50 mL) and HCl gas at 0°C for 35 minutes (1.56 g, 99%). FAB-MS calc. for C₂₅H₃₀N₄O₃:434; Found 435 (M+H)

15

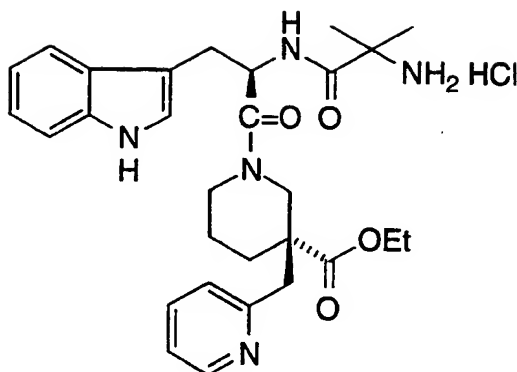
Step E:

Prepared by the procedure described in Example C1, Step D from the intermediate prepared in Step D of this example (1.5 g, 2.96 mmol), N-t-Boc-α-methylalanine (1.1 eq.) DMAP (0.15 eq.), N-methyl morpholine (1 eq.), and EDC (1.135 g, 5.92 mmol). Purification by MPLC provided the title compound. (1.488g, 81%)

30

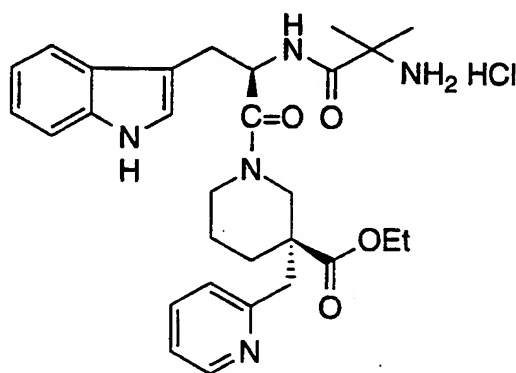
FAB-MS calc. for C₃₄H₄₅N₅O₆: 619; Found 620 (M+H)

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Step F:

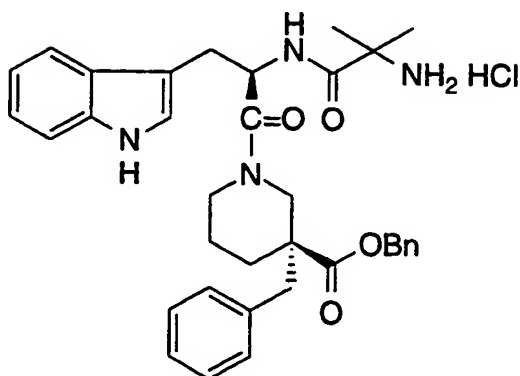
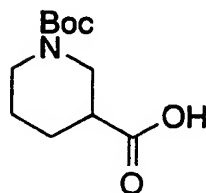
Prepared by the procedure described in Example C1, Step C from the intermediate from Step E (1.40 g, 2.26 mmol) in ethyl acetate (100 mL) and HCl gas at 0°C for 1 hour (1.388 g, 100%).

¹H NMR (CD₃OD, 400 MHz): 8.79-8.78 (M, 1H), 8.56-8.48 (M, 2H), 8.0-7.96 (M, 1H), 7.72 (d, J=8.21 Hz, 1H) 7.53 (d, J=7.98 Hz, 1H) 7.25-7.22 (M, 2H) 6.89-6.86 (M, 1H) 5.48-5.43 (M, 1H) 3.89 (t, J=7.1 Hz, 2H) 2.30 (d, J=14.3 Hz, 1H) 1.85 (d, J=14.4 Hz, 1H) 1.01 (t, J=7.1 Hz, 3H) FAB-MS calc. for C₂₉H₃₇N₅O₄: 519; Found 520 (M+H)

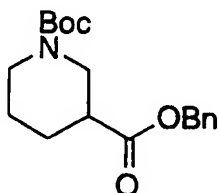
EXAMPLE C9

The title compound was similarly prepared from the intermediate d2 from Example C8, Step A. FAB-MS calc. for C₂₉H₃₇N₅O₄: 519; Found 520 (M+H)

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EXAMPLE C10Step A:

To a stirred solution of nipecotic acid (5 g, 38.7 mmol) in NaOH (2 eq.) in water was added di-tert-butyl dicarbonate (10 g, 46.44 mmol). The mixture was stirred at room temperature for 2 days. The mixture was then slowly acidified to pH=3 and stirred for two hours. The solution was extracted with ethyl acetate, dried, and concentrated to give white solid (6.25 g, 70%).

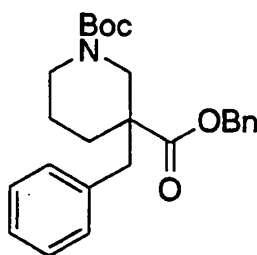
Step B:

To a solution of the intermediate from the previous step (6.25 g, 27.3 mmol), benzyl alcohol (3.4 mL, 32.7 mmol) and DMAP (33 mg, 0.273 mmol) in dichloromethane at 0°C, was added EDC (6.9 g, 35.4 mmol). The reaction mixture was stirred at room temperature for 7

- 291 -

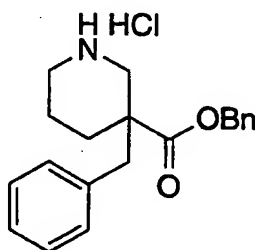
hours. It was washed with a mixture of brine and 3 N HCl, dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by silica gel flash column eluting with a gradient of 10-30% ethyl acetate in hexane provided the benzyl ester (7.41 g, 85%).

Step C:



Prepared by the procedure described in Example C1, Step B from benzyl N-t-Boc-nipecotate (7.12 g, 22.2 mmol), LHMDS in THF (33.3 mL, 33.3 mmol) and benzyl bromide (4.0 g, 33.3 mmol). Purification by silica gel flash column chromatography eluting with 5-20% ethyl acetate in hexane provided the title compound. (9.10 g, 100%) ¹H NMR (CDCl₃, 400MHz) δ 7.33-7.28 (m, 3 H), 7.23-7.17 (m, 5 H), 7.01-6.98 (m, 2 H), 5.00 (br. ABq, JAB = 12 Hz, 2 H), 4.00 (br. s, 1 H), 3.55-3.50 (m, 1 H), 3.18 (d, J = 13 Hz) 3.14 (v. br. s, 1 H), 2.92 (d, J = 13.5 Hz), 2.74 (d, J = 13.4 Hz), 2.03-1.99 (m, 1 H), 1.63-1.50 (m, 3H), 1.39 (s, 9 H).

Step D:



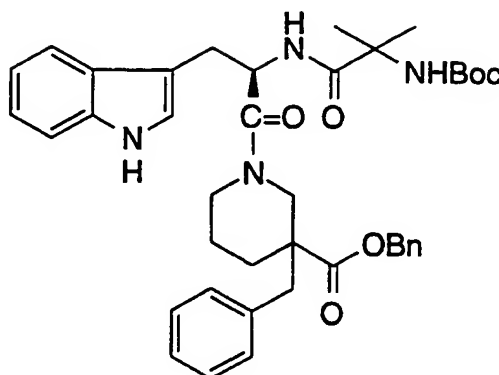
Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (3.08 g, 7.52 mmol) in ethyl acetate (40 mL) and HCl gas at 0°C for 15 minutes (2.65 g, 100%).

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FAB-MS calc. for $C_{20}H_{23}NO_2$: 309; Found 310 (M+H)Step E:

5

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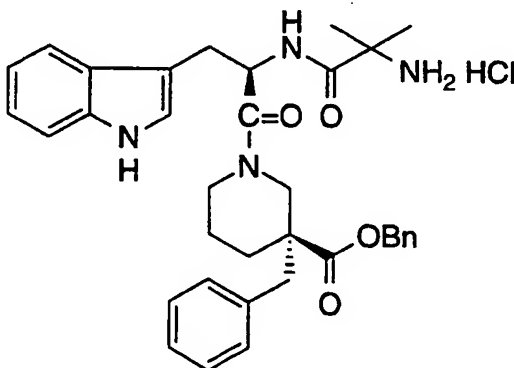


Prepared by the procedure described in Example C1, Step D
from the intermediate prepared in the previous step (768 mg, 2.22 mmol),
Intermediate 1 (720 mg, 1.85 mmol), HOBT (1 eq.), N-methyl
morpholine (1 eq.), and EDC (2 eq.). Purification by MPLC, eluting with
50% ethyl acetate in hexane, provided two diastereomers. The isomer
which came out first was designated as d1 (504 mg, 40%) and the one
which eluted second was designated as d2 (474 mg, 38%)
d1 FAB-MS calc. for $C_{40}H_{48}N_4O_6$: 680; Found 681 (M+H)
d2 FAB-MS calc. for $C_{40}H_{48}N_4O_6$: 680; Found 681 (M+H)

Step F:

25

30



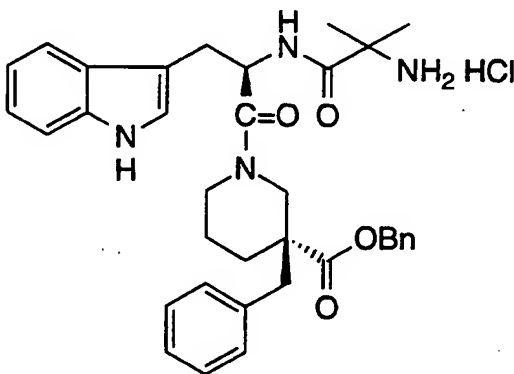
- 293 -

Prepared by the procedure described in Example C1, Step C from the intermediate d1 from Step E (25 mg, 0.036 mmol) in ethyl acetate (3 mL) and HCl gas at 0°C for 10 minutes (20.2 mg, 91%).
FAB-MS calc. for C₃₅H₄₀N₄O₄: 580; Found 581 (M+H)

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EXAMPLE C11

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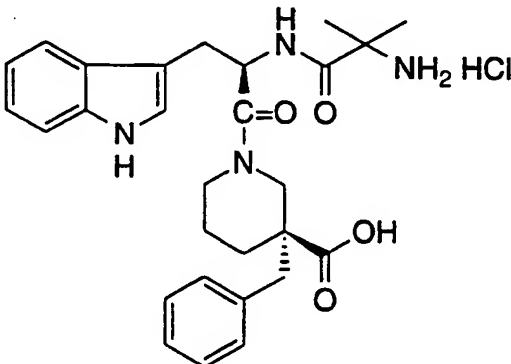
Prepared by the procedure described in Example C1, Step C from the intermediate d2 (20.1 mg, 0.03 mmol) of Example C10, Step E in ethyl acetate (3 mL) and HCl gas at 0°C for 10 minutes (12.8 mg, 70%).

20

FAB-MS calc. for C₃₅H₄₀N₄O₄: 580; Found 581 (M+H)

EXAMPLE C12

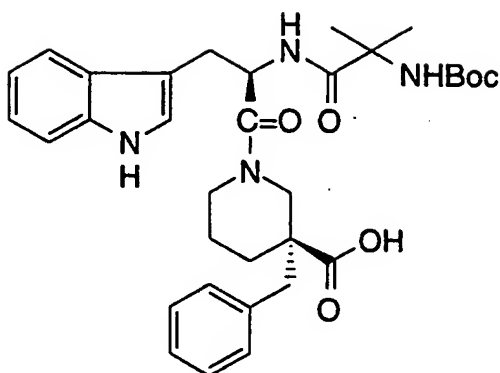
25



30

Step A:

- 294 -



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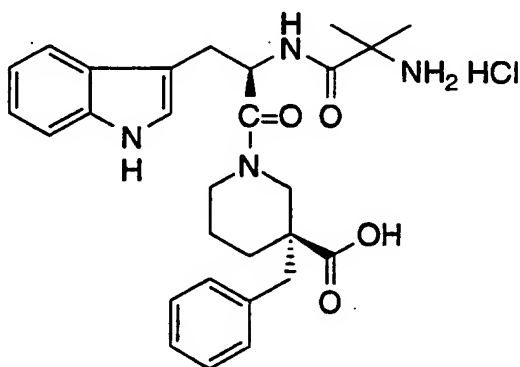
10

A suspension of 10% palladium on carbon (60 mg) and the intermediate (d1) from Example C10, Step E (442.6 mg, 0.65 mmol) in ethanol (20 mL) was vigorously stirred under a hydrogen atmosphere for 30 minutes. The reaction mixture was then filtered through celite and evaporated to give the product (376.0 mg, 98%).

15

d1 FAB-MS calc. for $C_{33}H_{42}N_4O_6$: 590; Found 591 (M+H)

Step B:



20

25

Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (211 mg, 0.357 mmol) and HCl gas in ethyl acetate (15 mL) at 0°C for 10 minutes (175.6 mg, 93%). 1H NMR (CD_3OD , 400MHz): The compound exists in two rotamers in approximately a 1:1 ratio. δ 7.57-7.54 (m, 1 H), 7.38 (d, $J = 8.2$ Hz, 1/2 H), 7.33 (d, $J = 8.2$ Hz, 1/2 H), 7.25-7.00 (m, 8 H), 6.81-6.79 (m, 1 H), 5.36 (dd, $J = 6$ Hz, 8.5 Hz, 1/2 H), 5.18 (app t, $J = 7.5$ Hz, 1/2 H), 4.32 (br. d, $J = 13$ Hz, 1/2 H), 4.00 (br. d, $J = 13$ Hz, 1/2 H), 3.78 (br. d, $J = 13$

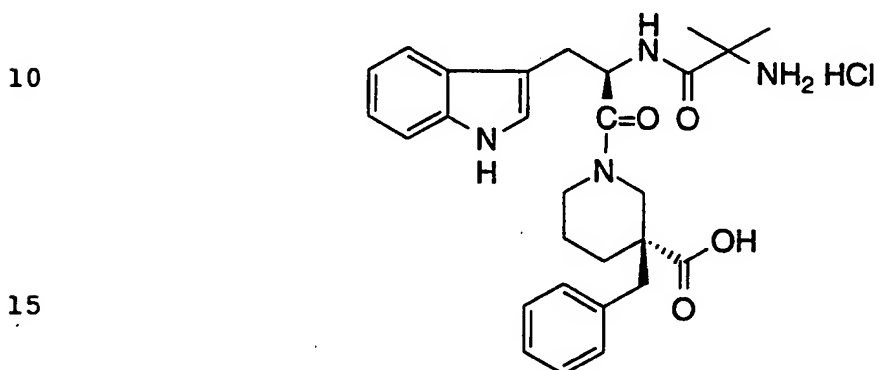
30

- 295 -

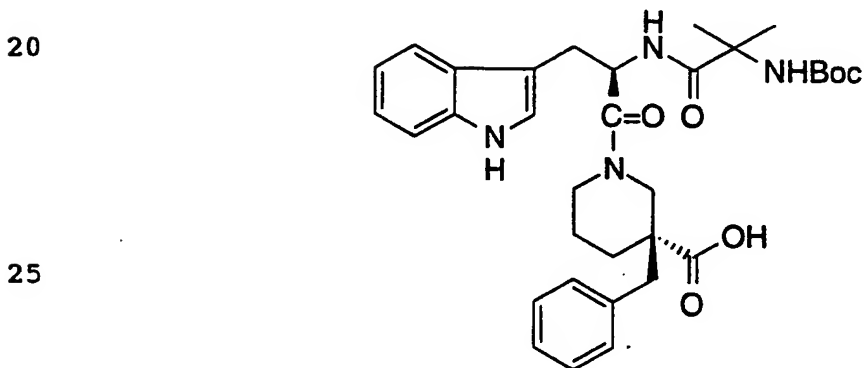
Hz, 1/2 H), 3.26-3.02 (m, 11/2 H), 2.86 (d, J = 13.4 Hz, 1/2 H), 2.80 (d, J = 13.4 Hz, 1/2 H), 2.53 (d, J = 13.4 Hz, 1/2 H), 2.46 (d, J = 13.4 Hz, 1/2 H), 2.29 (dt, 1/2 H), 2.09 (d, J = 12.7 Hz, 1/2 H), 1.92-1.88 (m, 1/2 H), 1.55, 1.50, 1.44 (3s, 6 H), 1.40-1.25 (m, 1 H), 1.20-1.12 (m, 1/2 H).

5. d1 FAB-MS calc. for C₂₈H₃₄N₄O₄: 490; Found 491 (M+H)

EXAMPLE C13

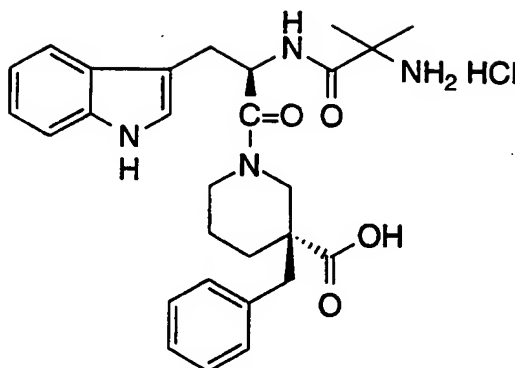


Step A:



Prepared similarly from the intermediate d2 (224.2 mg, 0.33 mmol) from Example C10, Step E (169.3 mg, 87%).
d2 FAB-MS calc. for C₃₃H₄₂N₄O₆: 590; Found 591 (M+H)

- 296 -

Step B:

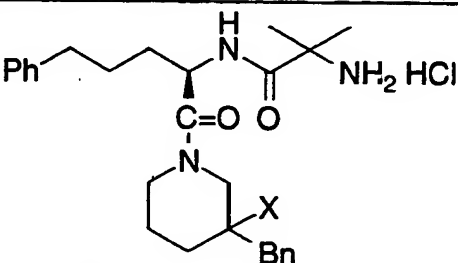
Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (139 mg, 0.235 mmol) and HCl gas in ethyl acetate (15 mL) at 0°C for 10 minutes (122.7 mg, 99%).

¹H NMR (CD₃OD, 400MHz): The compound exists as two rotamers in approximately a 1:1 ratio. δ 8.21 (d, J = 7.4 Hz, 1/2 H), 7.91 (d, J = 7.4 Hz, 1/2 H), 7.62 (d, J = 7.9 Hz, 1/2 H), 7.50 (d, J = 7.9 Hz, 1/2 H), 7.34-6.90 (m, 9 H), 5.40-5.34 (m, 1 H), 4.40 (d, J = 13.7 Hz, 1/2 H), 4.13 (d, J = 12.6 Hz, 1/2 H), 3.63 (d, J = 13.3 Hz, 1/2 H), 3.50 (d, J = 13.3 Hz, 1/2 H), 3.30-3.10 (m, 7/2 H), 2.93 (ABq, 1H), 2.88 (v. br. d, 1/2 H), 2.60 (d, J = 13 Hz, 1/2 H), 2.40 (d, J = 13 Hz, 1/2 H), 2.19-2.16 (m, 1/2 H), 1.78-1.75 (m, 1 H), 1.60-1.40 (m, 3/2 H), 1.20-1.10 (m, 1/2 H), 1.58, 1.50, 1.47, 1.15 (4s, 6 H), 1.00-0.90 (m, 1/2 H).

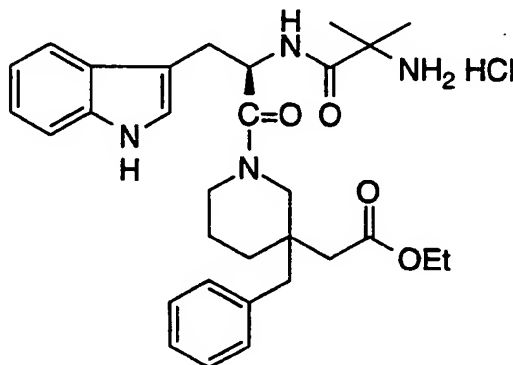
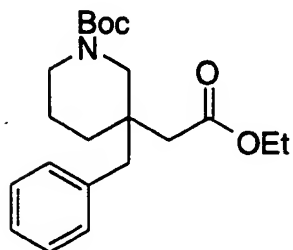
d2 FAB-MS calc. for C₂₈H₃₄N₄O₄: 490; Found 491 (M+H)

The additional examples shown in Table CV were prepared according to Examples C10 through C12 using Intermediate 3 and the intermediate obtained in Example C10 Step D.

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TABLE CV: ADDITIONAL EXAMPLES


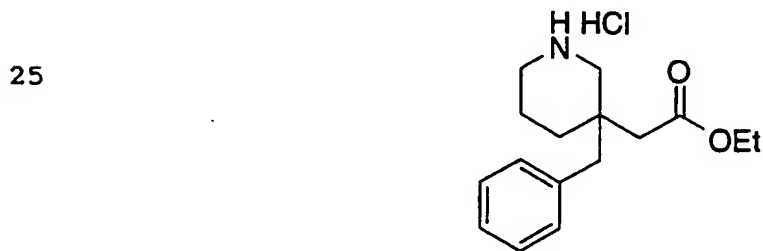
| entry | X | MF | isomer |
|-------|--------------------|--|--------|
| | | FAB-MS (M+1) | |
| 1 | CO ₂ Bn | C ₃₅ H ₄₃ N ₃ O ₄ 570 | RS |
| 2 | CO ₂ H | C ₂₈ H ₃₇ N ₃ O ₄ 480 | RS |

EXAMPLE C14Step A:

A solution of n-BuLi in hexane (4.9 mL, 12.36 mmol) was added to a stirred solution of 2,2,6,6-tetramethylpiperidine (TMP, 2.3 mL, 1.92 g, 13.5 mmol) in THF (25 mL) with ice-bath cooling. In a

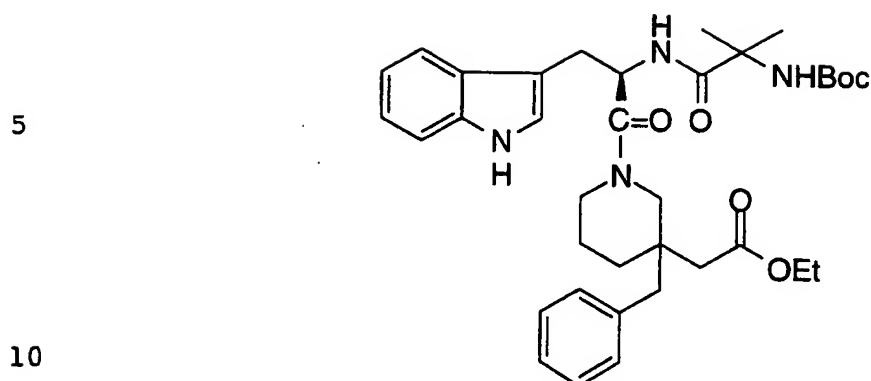
- 298 -

separate flask, a stirred mixture of ethyl N-t-Boc-3-benzyl-nipecotate (Example C1, Step B, 1.73 g, 5 mmol) and CH_2Br_2 (0.78 mL, 2.15 g, 12.4 mmol) in THF (20 mL) was cooled to -78°C , and the Lithium salt solution of TMP solution just prepared was then added over a 15 minute
5 period at a temperature below -65°C . After 10 minute, a solution of LHMDs (11.2 mL, 11.2 mmol) was added over a 10 minutes period at -78°C . Following the addition, the cooling bath was removed and the mixture was allowed to warm gradually to 0°C . The mixture was cooled with an ice bath, and a solution of n-BuLi in hexane (13.5 mL, 33.7
10 mmol) was added at a temperature below 5°C over a 15 minutes period. The mixture was warmed to room temperature and stirred for 45 minutes. The mixture was cooled to -78°C and quenched over a 50 minute period by adding it into a stirred solution of acidic ethanol (30 mL) at 0°C . The mixture was evaporated to dryness and suspended in dichloromethane
15 (100 mL), to which was added triethylamine (0.7 mL, 5.0 mmol) and di-tert-butyl dicarbonate (1.09 g, 5.0 mmol) while stirring. After 1 hour of stirring at room temperature, the material was washed with brine, dried, and concentrated. Purification by silica gel flash column chromatography, eluting with 10-30% ethyl acetate in hexane, provided
20 the compound (1.44 g, 80%).

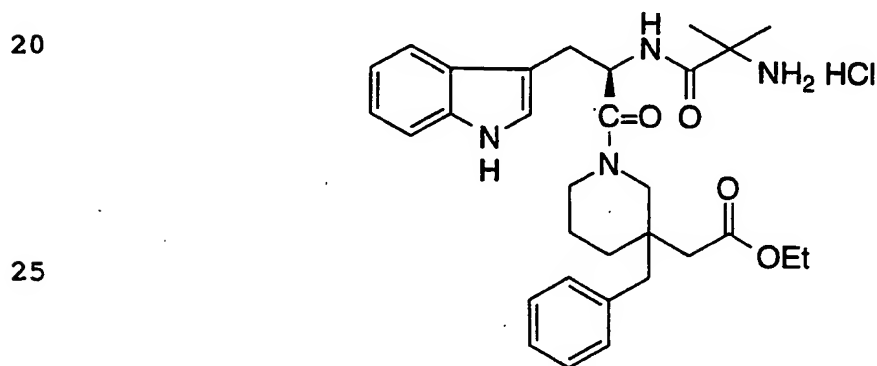
Step B:

30 Prepared by the procedure described in Example C1, Step C, from the intermediate from the previous step (1.30 g, 3.56 mmol) and HCl gas in ethyl acetate (50 mL) at 0°C for 45 minutes (975 mg, 91%). FAB-MS calc. for $\text{C}_{16}\text{H}_{23}\text{NO}_2$: 261; Found 262 (M+H)

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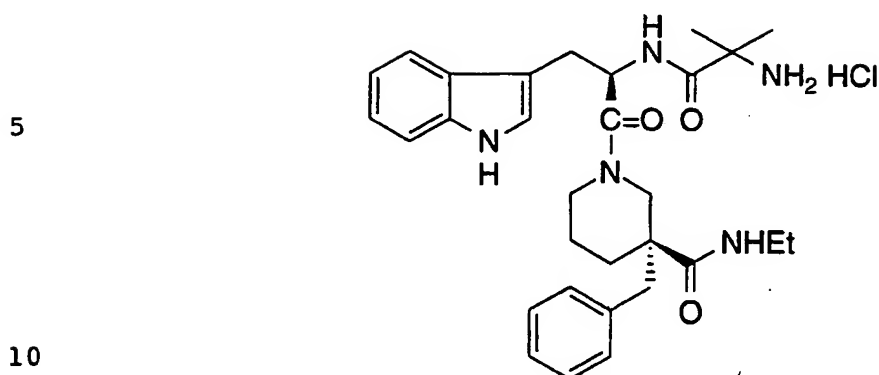
Step C:

Prepared by the procedure described in Example C1, Step D from the intermediate prepared in the previous step (55 mg, 0.21 mmol), Intermediate 1 (1 eq.), HOBT (1 eq.), N-methyl morpholine (1 eq.), and EDC (80 mg, 0.42 mmol). Purification by MPLC eluting with 60% ethyl acetate in hexane provided the compound (77 mg, 61.5%).

Step E:

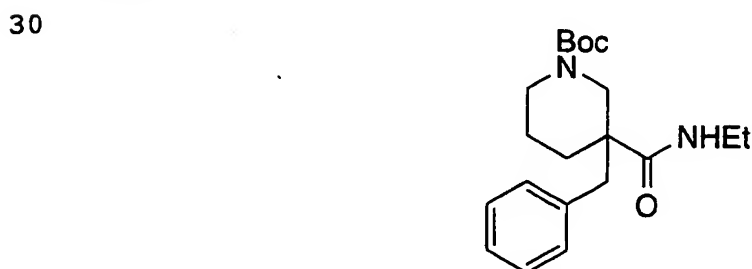
Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (77 mg, 0.13 mmol) and HCl gas in ethyl acetate (8 mL) at 0°C for 15 minutes (59 mg, 85%). FAB-MS calc. for C₃₁H₄₀N₄O₄: 532; Found 533 (M+H)

- 300 -

EXAMPLE C15Step A:

The intermediate from Example C10, Step C (1.85g, 4.52 mmol) was hydrogenated over 1 atm of H₂ and 10% palladium on carbon (150 mg) in ethanol (20 mL). Filtering through celite and evaporation yielded the acid (1.36 g, 94%). ¹H NMR (CDCl₃, 400 MHz) δ 7.27-7.19 (m, 3 H), 7.14-7.10 (m, 2 H), 4.08-3.59 (br. m, 1 H), 3.63-3.59 (m, 1 H), 3.15-3.05 (br. m, 2 H), 2.9. (d, J = 13.5 Hz, 1 H), 2.79 (d, J = 13.5 Hz, 1 H), 2.05-1.95 (br. m, 1 H), 1.70-1.45 (m, 3 H), 1.42 (s, 9 H). EI-MS calc. for C₁₈H₂₅NO₄: 319; Found 319 (M⁺).

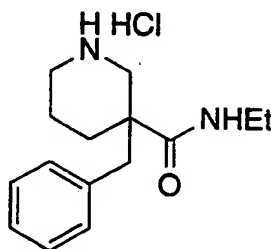
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Step B:

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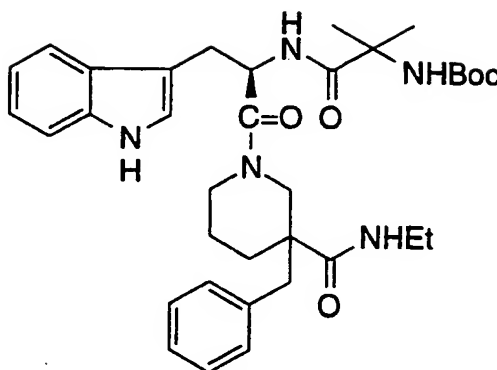
To a solution of the intermediate from the previous step (320.4 mg, 1.0 mmol) in dichloromethane containing ethyl amine hydrochloride (163 mg, 2.0 mmol), DMAP (1.0 eq.), and N-methyl morpholine (2 eq.), was added EDC (2 eq.). The reaction mixture was stirred at room temperature overnight. The solution was washed with 3 N HCl and brine, dried over anhydrous magnesium sulfate, then filtered and concentrated. Purification by silica gel flash column eluting with a gradient of 60-100% ethyl acetate in hexane provided the title compound (262 mg, 76%). ¹H NMR (CDCl₃, 400 MHz) δ 7.21-7.13 (m, 3 H), 7.03 (d, 2 H), 6.68 (br. s, 1 H), 4.18 (br. d, 1 H), 3.96 (br. d, 1 H), 3.12-3.00 (m, 4 H), 2.70-2.40 (br. m, 5 H), 1.60-1.50 (m, 1 H), 1.37 (s, 9 H), 1.20-1.30 (m, 1H), 0.90 (q, J = 7.3 Hz, 3 H). EI-MS calc. for C₂₀H₃₀N₂O₃: 346; Found 346 (M⁺)

Step C:



Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (262 mg, 0.76 mmol) and HCl gas in ethyl acetate (5 mL) at 0°C for 1 hour (194 mg, 90%). ¹H NMR (CD₃OD, 400MHz) δ 8.28 (br. s, 1 H), 7.30-7.24 (m, 3 H), 7.14-7.12 (m, 2 H), 3.43 (d, J = 12 Hz, 1 H), 3.34-3.28 (m, 2 H), 3.26-3.20 (br. d, 1 H), 3.11 (d, J = 14 Hz, 1 H), 2.88 (dt, J = 3.2 Hz, 13 Hz, 1H), 2.81 (d, J = 12.5 Hz, 1 H), 2.77 (d, J = 14 Hz, 1 H), 2.24 (d, J = 13 Hz, 1 H), 1.87 (td, J = 2.8 Hz, 14 Hz, 1 H), 1.75 (dt, J = 3.3 Hz, 13.5 Hz, 1 H), 1.64-1.55 (m, 1 H), 1.17 (t, J = 7 Hz, 3 H).

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Step D:

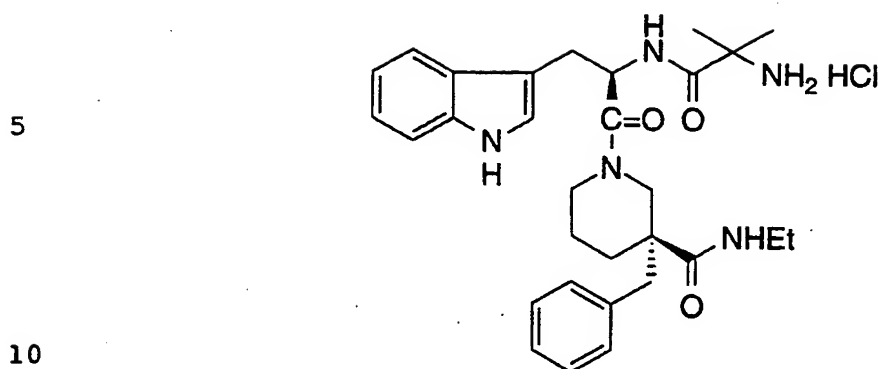
Prepared by the procedure described in Example C1, Step D from intermediate prepared in the previous step (62.2 mg, 0.22 mmol), Intermediate 1 (1 eq.), HOBT (1 eq.), N-methyl morpholine (1 eq.), and EDC (2 eq.). Purification by MPLC eluting with ethyl acetate provided two diastereomers, the one which was eluted out of the column first was designated as d1 (35.8 mg, 26%) and the one came out second was designated as d2 (43.8 mg, 31%).

d2. ^1H NMR (CD_3OD , 400 MHz): The compound exists in two rotamers in approximately a 1:1 ratio. δ 8.16 (br. s, 1/2 H), 7.53 (d, J = 8.7 Hz, 1 H), 7.32 (d, J = 8.1 Hz, 1 H), 7.25-6.96 (m, 8 H), 6.69 (br. s, 1/2 H), 5.28-5.12 (m, 1/2 H), 4.94 (v. br. m, 1/2 H), 4.31 (br. d, J = 14.6 Hz, 1/2 H), 3.49 (v. br. d, J = 13 Hz, 1/2 H), 3.22 (dd, J = 4.7 Hz, 14.3 Hz, 1/2 H), 3.03-2.97 (m, 2 H), 2.90 (d, J = 13.4 Hz, 1/2 H), 2.40 (br. d, 1/2 H), 2.36 (d, J = 13.3 Hz, 1/2 H), 2.10 (d, J = 13.5 Hz, 1/2 H), 1.92-1.82 (br. m, 3/2 H), 1.47 (s, 3 H), 1.41 (s, 9 H), 1.38 (s, 3 H), 1.32-1.20 (m), 1.10-1.00 (dt, 1/2 H), 0.85 (t, J = 7.2 Hz, 3 H).

d1 FAB-MS calc. for $\text{C}_{35}\text{H}_{47}\text{N}_5\text{O}_5$: 617; Found 618 ($\text{M}+\text{H}$)

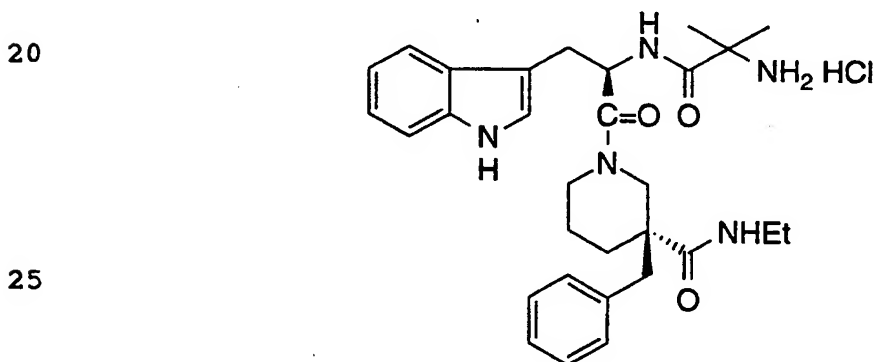
d2 FAB-MS calc. for $\text{C}_{35}\text{H}_{47}\text{N}_5\text{O}_5$: 617; Found 618 ($\text{M}+\text{H}$)

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Step E:

Prepared by the procedure described in Example C1, Step C from the Intermediate d1 from the previous step (35 mg, 0.057 mmol) and HCl gas in ethyl acetate (3 mL) at 0°C for 30 minutes (32.5 mg, 100%). FAB-MS calc. for C₃₀H₃₉N₅O₃: 517; Found 518 (M+H)

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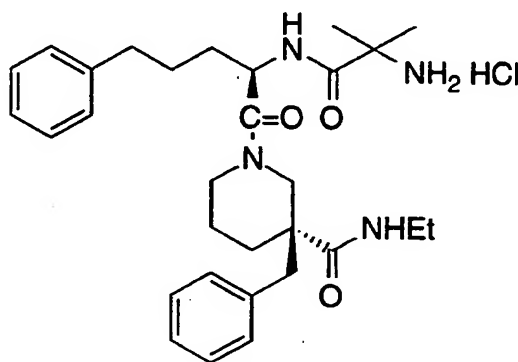
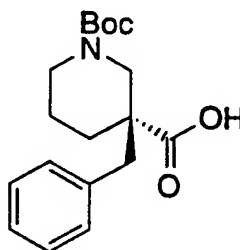
EXAMPLE C16

Prepared by the procedure described in Example C1, Step C from the intermediate d2 from Example C15, Step D (41 mg, 0.066 mmol) and HCl gas in ethyl acetate (3 mL) at 0°C for 30 minutes (36.5 mg, 100%). ¹H NMR (CD₃OD, 400 MHz): The compound exists in two rotamers in approximately a 4:1 ratio. δ 8.21 (d, J = 7.4 Hz, 4/5 H), 8.02 (d, J = 7.4 Hz, 1/5 H), 7.68 (d, J = 7.8 Hz, 1/5 H), 7.54 (d, J = 7.8 Hz, 4/5 H), 7.35 (d, J = 7.1 Hz, 4/5 H), 7.31 (d, J = 7.1 Hz, 1/5 H), 7.26-6.98 (m,

30

- 304 -

8 H), 5.46-5.40 (m, 1/5 H), 5.25-5.20 (m, 4/5 H), 4.00 (br. d, 4/5 H), 3.85 (br. d, 1/5 H), 3.65 (br. d, J = 13.2 Hz, 4/5 H), 3.60-3.54 (m, 1/5 H), 3.36 (br. d, 1/5 H), 3.30-3.03 (m), 2.99-2.90 (m), 2.82-2.62 (m), 2.46 (d, J = 13.3 Hz, 8/5 H), 2.08 (br. d, 4/5 H), 1.90-1.84 (m, 1/5 H), 1.76-1.65 (m), 1.51, 1.49 (2s, 6 H), 1.40-1.20 (m), 1.00 (t, J = 7.2 Hz, 3/5 H), 0.88 (t, J = 7.2 Hz, 12/5 H). FAB-MS calc. for C₃₀H₃₉N₅O₃: 517; Found 518 (M+H)

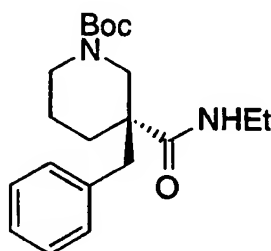
EXAMPLE C17Step A

To a suspension of the S- isomer intermediate of Step A of Example C2 (27.3 g, 68.8 mmol) in 3 N sodium hydroxide (25 mL), dichloromethane (200 mL) and water (100 mL), was slowly added di-*t*-butyl dicarbonate (18 g, 1.2 equiv.). The mixture was stirred for an additional 5 hours after the addition, it was acidified to pH 3 carefully and then extracted with ethyl acetate three times. The organic extracts were combined, dried, and concentrated to give a white solid (23.7 g).

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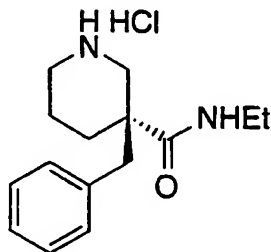
A solution of this intermediate (11.5 g, 33.1 mmol) and 3 N NaOH (30 mL) in ethanol (200 mL) and water (10 mL) was refluxed for one day. The solution was evaporated to remove ethanol, and then acidified with 3 N HCl to pH=3 and extracted with ethyl acetate. The extract was dried, evaporated and purified by a short silica gel column, initially eluting with 20% ethyl acetate in hexane, then with ethyl acetate to give the product (8.76 g, 83%). NMR and MS were identical to Example C15 stepA.

Step B



To a mixture of the intermediate from the previous step (660 mg, 2.07 mmol), ethylamine hydrochloride (251 mg, 1.5 equiv.), NMM (0.23 mL, 1 equiv.) and HOBT (1 eq) in dichloromethane and DMF (1:1, 10 mL) was added EDC. The mixture was stirred at room temperature for two days, heated at reflux for 2 hours, and was poured into a dilute HCl and brine mixture. It was extracted with ethyl acetate, and the organic layer was washed with dilute NaOH, dried and evaporated. Purification by flash column eluting with 20-80% ethyl acetate in hexane gave the product (540 mg, 75%). NMR and MS were identical to Example C15 Step B.

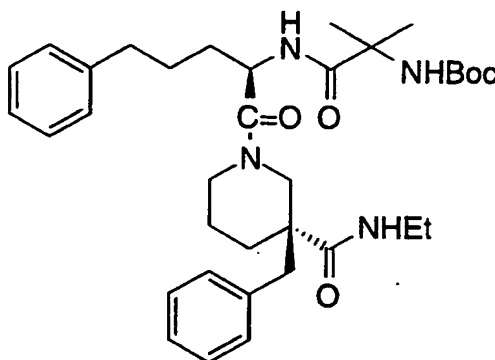
Step C



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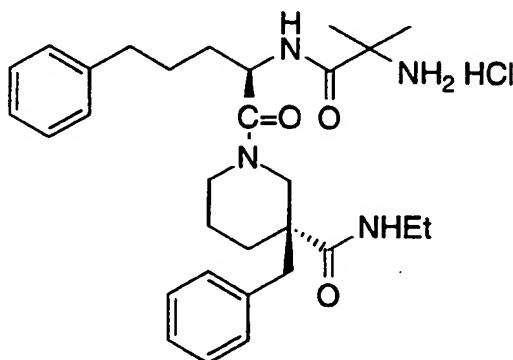
Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (0.33 g, 0.95 mmol) in ethyl acetate (5 mL) and HCl gas at 0°C for 15 minutes (0.279 mg, 100%). FAB-MS calc. for C₁₅H₂₂N₂O: 246 ; Found 247 (M+H)

Step D



Prepared by the procedure described in Example C1, Step D from the intermediate prepared in the previous step (100 mg, 0.354 mmol), Intermediate 3 (134 mg, 0.354 mmol), HOBT (48 mg, 1 eq.), N-methyl morpholine (0.039 mL, 1 eq.), and EDC (102 mg, 1.5 eq.). Purification by MPLC, eluting with ethyl acetate, provided the intermediate (140 mg, 65%). FAB-MS calc. for C₃₅H₅₀N₄O₅: 606 ; Found 607 (M+H)

Step E



Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (132 mg, 0.217 mmol) and HCl gas in ethyl acetate (5 mL) at 0°C for 10 minutes (113.3 mg, 96%).

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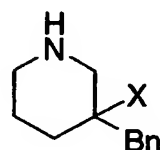
d1 FAB-MS calc. for C₃₀H₄₂N₄O₃: 506, Found: 507 (M+H)

The additional intermediates shown in Table CVIa were prepared according to the above established procedure as exemplified in Example C15, and Example C17 steps A through C,. The final compounds were prepared according to Example C17 Steps D and E, using Intermediate 1.

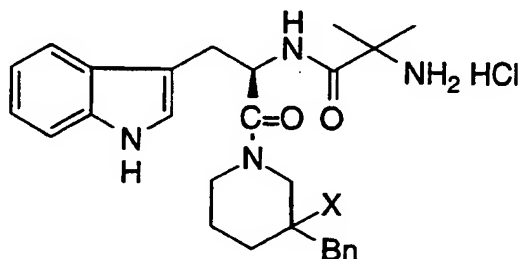
TABLE CVIa: ADDITIONAL EXAMPLES

10

15



Intermediate



Product

20

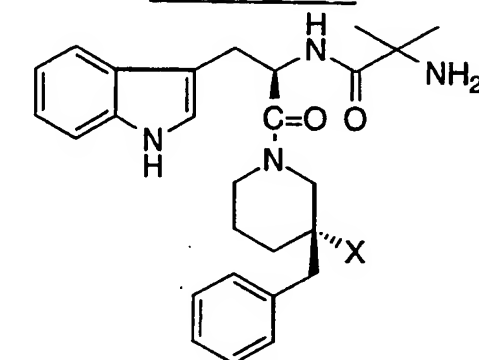
25

30

| | | Intermediate | | Product | |
|-------|--|--|--|---------|----------|
| entry | X | MF | MF | MF | isomer |
| | | FAB-MS (M+1) | FAB-MS (M+1) | | |
| 1 | -CO(morpholino) | C ₁₇ H ₂₄ N ₂ O ₂ 288 (M ⁺ , EI) | C ₃₂ H ₄₁ N ₅ O ₄ 560 | | S |
| 2 | -CONHCH ₃ | C ₁₄ H ₂₀ N ₂ O 233 | C ₂₉ H ₃₇ N ₅ O ₃ 504 | | S |
| 3 | -CONH- CH ₂ CO ₂ Et | C ₁₇ H ₂₄ N ₂ O ₃ 304 (M ⁺ , EI) | C ₃₂ H ₄₁ N ₅ O ₅ 576 | | S |
| 4 | -CO ₂ CH ₂ CO ₂ Et | C ₁₇ H ₂₃ NO ₄ 306 | C ₃₂ H ₄₀ N ₄ O ₆ 577 | | R S |
| 5 | -CO ₂ (CH ₂) ₂ SMe | C ₁₆ H ₂₃ NO ₂ S 294 | C ₃₁ H ₄₀ N ₄ O ₄ S 565 | | R S |
| 6 | -CON(CH ₃) ₂ | C ₁₅ H ₂₂ N ₂ O 247 | C ₃₀ H ₃₉ N ₅ O ₃ 518 | | d1 d2 |
| 7 | -CONH- (CH ₂) ₂ OH | C ₁₅ H ₂₂ N ₂ O ₂ 263 | C ₃₀ H ₃₉ N ₅ O ₄ 534 | | S |

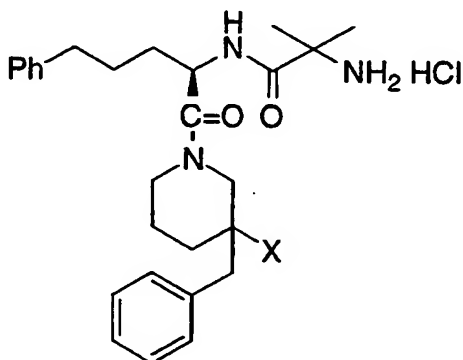
- 308 -

Likewise using 3-aminopropanol or 2-(ethylthio)ethylamine it is possible to prepare the compounds shown in Table CVIb using Intermediate 1.

TABLE CVIb

| entry | X |
|-------|---|
| 1 | -CONH(CH ₂) ₃ OH |
| 2 | -CONHCH ₂ CH ₂ SCH ₃ |

The additional compounds shown in Table CVIc were prepared according to Example 17 Steps C and D, using some of the intermediates shown in Table CVIa and Intermediate 3.

TABLE CVIc: ADDITIONAL EXAMPLES

| entry | Y | MF FAB-MS (M+1) | isomer |
|-------|---|--------------------|--------|
|-------|---|--------------------|--------|

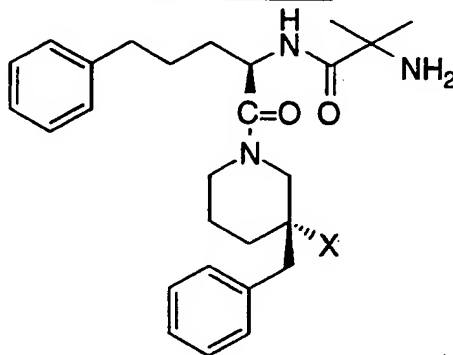
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| | | | | |
|---|---|--|--|---|
| | 1 | -CO(morpholino) | C ₃₂ H ₄₄ N ₄ O ₄ 549 | S |
| | 2 | -CONHCH ₃ | C ₂₉ H ₄₀ N ₄ O ₃ 493 | S |
| 5 | 3 | -CONH- CH ₂ CO ₂ Et | C ₃₂ H ₄₄ N ₄ O ₅ 565 | S |
| | 4 | -CONH- (CH ₂) ₂ OH | C ₃₀ H ₄₂ N ₄ O ₄ 523 | S |

10 Likewise using 3-aminopropanol and 2-(methylthio)-ethylamine it is possible to prepare the compounds shown in Table CVId.

TABLE CVId

15



20

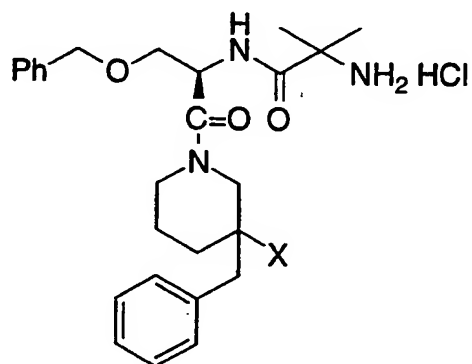
| entry | X |
|-------|---|
| 1 | -CONH(CH ₂) ₃ OH |
| 2 | -CONHCH ₂ CH ₂ SCH ₃ |

25

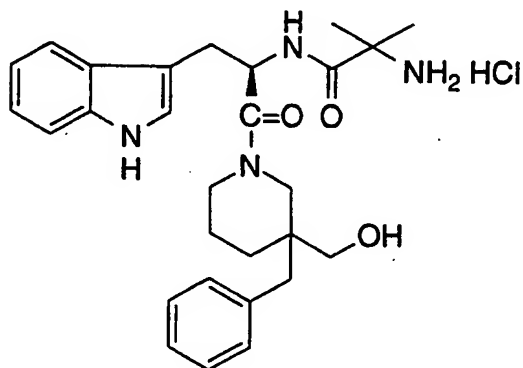
The additional compounds shown in Table CVIe were prepared according to Example 17 Steps C and D, using some of the intermediates shown in Table CVI and Intermediate 2.

30

- 310 -

TABLE CVIe: ADDITIONAL EXAMPLES

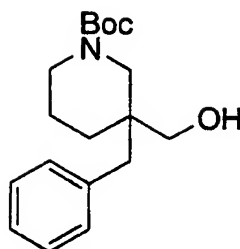
| entry | Y | MF | isomer |
|-------|--|--|--------|
| | | FAB-MS (M+1) | |
| 1 | -CO(morpholino) | C ₃₁ H ₄₂ N ₄ O ₅ 551 | S |
| 2 | -CONHCH ₃ | C ₂₈ H ₃₈ N ₄ O ₄ 495 | S |
| 3 | -CONH- CH ₂ CO ₂ Et | C ₃₁ H ₄₂ N ₄ O ₆ 567 | S |

EXAMPLE C18

- 311 -

Step A:

5

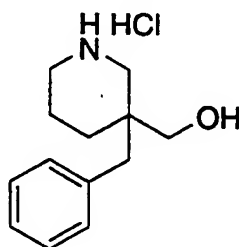


10 To a stirred solution of ethyl N-t-Boc-3-phenylmethyl nipecotate (10.4 g, 29.93 mmol) in dichloromethane (100 mL) at -78°C was added DIBAL (1M, 45 mL). The reaction was stirred at -78°C for 4 hours and quenched by the addition of methanol (5 mL). The reaction mixture was washed carefully with tartaric acid water solution and brine, dried over MgSO₄ and evaporated. Silica gel flash chromatography
15 eluting with a gradient of 40-80% ethyl acetate in hexane yielded the product (6.81 g, 75%).

EI-MS calc. for C₁₈H₂₇NO₃: 305; Found 305 (M⁺)

20 Step B: 3-Phenylmethyl-3-piperidinemethanol hydrochloride

25



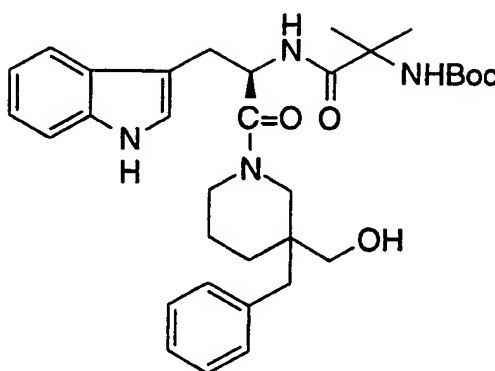
A solution of the intermediate from the previous step (770 mg, 2.52 mmol) in ethanol (20 mL) and concentrated HCl (1 mL) was refluxed for 3 hours. The reaction mixture was cooled to room
30 temperature and evaporated to give the title compound as a white solid. (609.0 mg, 100%)

¹H NMR (CD₃OD, 400 MHz) δ 7.31-7.19 (m, 5 H), 3.45 (ABq, J = 11 Hz, 2 H), 3.18 (d, J = 13 Hz, 1 H), 3.19-3.13 (m, 1 H), 3.03-2.99 (m, 1 H), 2.96 (d, J = 13 Hz, 1 H), 2.72 (s, 1 H), 1.92-1.84 (m, 2 H), 1.60-1.50 (m, 2 H).

- 312 -

EI-MS calc. for $C_{12}H_{17}NO$: 191; Found 191 (M^+)

Step C:



Prepared by the procedure described in Example C1, Step D

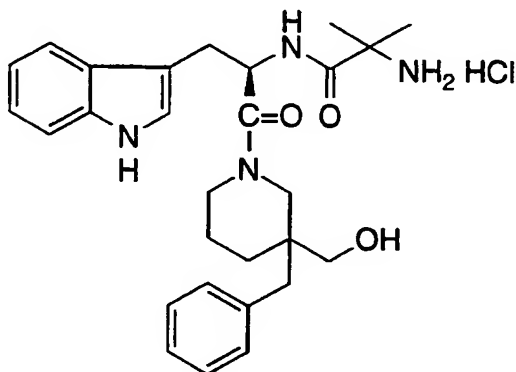
15 from the intermediate prepared in the previous step (142 mg, 0.587 mmol), Intermediate 1 (0.8 eq.), HOBT (1 eq.), N-methyl morpholine (1 eq.), and EDC (2 eq.). Purification by MPLC eluting with ethyl acetate gave two compounds; the compound which came out of the column first is designated as d1 (98.5 mg, 58%) and the compound which came out of

20 the column next as d2 (34.5 mg, 12%)

d1 FAB-MS calc. for $C_{32}H_{42}N_4O_5$: 562; Found 563 ($M+H$)

d2 FAB-MS calc. for $C_{32}H_{42}N_4O_5$: 562; Found 563 ($M+H$)

Step D:

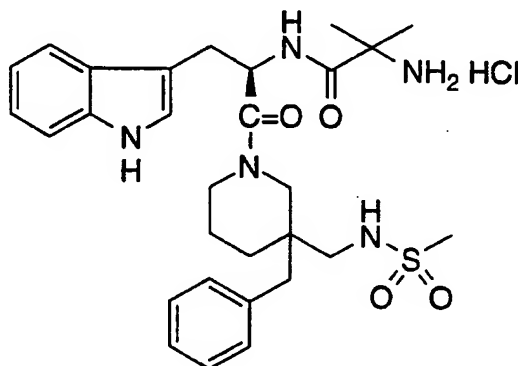


- 313 -

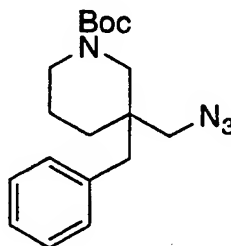
The intermediate (d1) from the previous step (60 mg, 0.104 mmol) was treated with HCl gas at 0°C in ethyl acetate (3 mL) for five minutes. Evaporation gave the diastereomer 1 of the title compound.
d1 FAB-MS calc. for C₂₈H₃₆N₄O₃: 476; Found 477 (M+H)

The intermediate (d2) from Step C (20 mg) was treated with HCl gas at 0°C in ethyl acetate (3 mL) for five minutes. Evaporation gave the diastereomer 2 of the title compound.
d2 FAB-MS calc. for C₂₈H₃₆N₄O₃: 476; Found 477 (M+H)

EXAMPLE C19



Step A:



To a stirred solution of intermediate from Example C18, Step A (5.12 g, 16.8 mmol), and triethylamine (4.7 mL) in dichloromethane at 0°C was added mesyl chloride (1.95 mL). The reaction mixture was stirred for 2 hours. The solution was poured into a mixture of brine and 3 N HCl and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, dried over

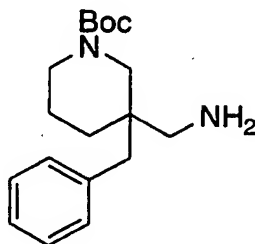
- 314 -

magnesium sulfate and evaporated to yield the mesylate. The mesylate was heated with sodium azide (2.2 g, 33.6 mmol) in DMSO (20 mL) at 80°C for two weeks. The mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate and brine; it was dried, and evaporated. Purification by silica gel flash column chromatography provided the azide (4.14 g, 75%).

¹H NMR (CDCl₃, 200 MHz) δ 7.29-7.13 (m, 5 H), 3.61-3.57 (br. m, 1 H), 3.47 (d, J = 12 Hz, 1 H), 3.20-3.10 (v. br. s, 2 H), 3.10-2.96 (v. br. d, 1 H), 2.60-2.45 (br. m, 2 H), 1.65-1.48 (m, 4 H), 1.44 (s, 9 H), 1.41-1.35 (m, 1 H).

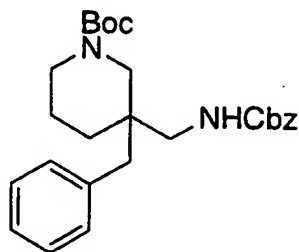
FAB-MS calc. for C₁₈H₂₆N₄O₂: 330; Found 331 (M+H)

Step C:



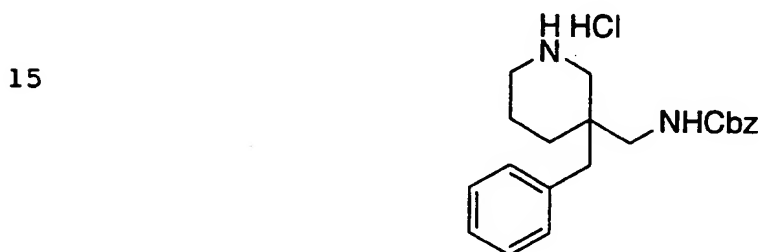
The azide from the previous step (1.60 g, 4.84 mmol) was hydrogenated over 10% palladium on carbon (160 mg) in ethanol (25 mL) under a 1 atm hydrogen balloon for 2 hours. The reaction mixture was filtered through celite and evaporated to give the amine (1.42 g, 96%). FAB-MS calc. for C₁₈H₂₈N₂O₂: 304; Found 305 (M+H)

Step D:



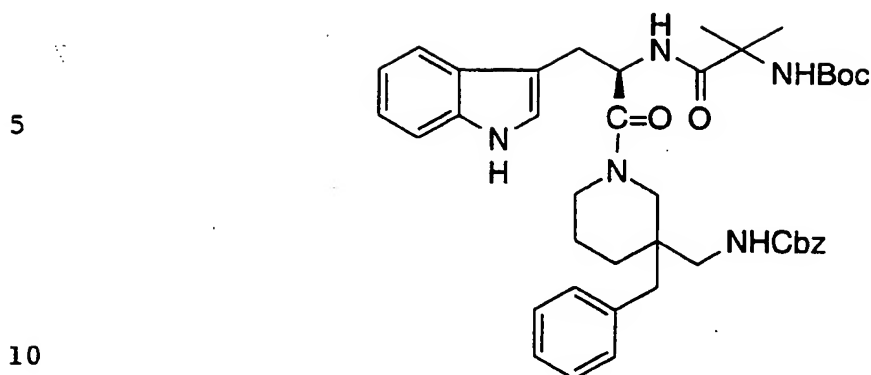
- 315 -

To a stirred solution of the amine from the previous step (1.30 g, 4.27 mmol) in dichloromethane (20 mL) which also contained DMAP (20 mg) and triethylamine (1 mL) at 0°C, was added CbzCl (0.73 mL, 5.12 mmol). The reaction mixture was stirred for 2 hours. The solution was poured into a mixture of brine and 3 N HCl and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, dried over magnesium sulfate and evaporated to give a residue which was purified by flash chromatography, eluting with 20% ethyl acetate in hexane, to yield the product (1.52 g).
FAB-MS calc. for C₂₆H₃₄N₂O₄: 438; Found 439 (M+H)

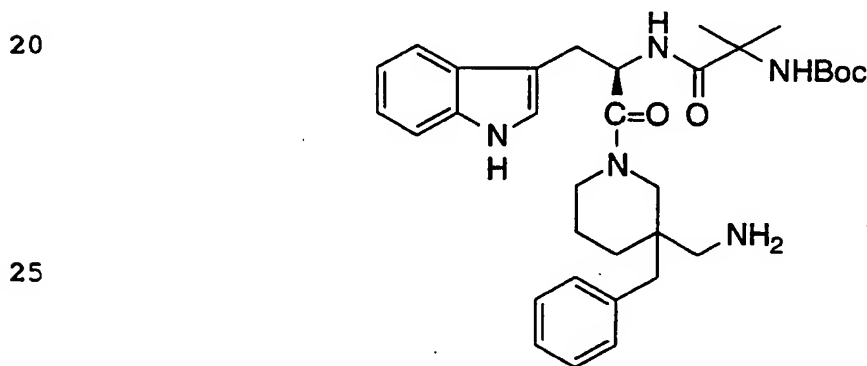
Step E:

To a stirred solution of the intermediate from the previous step (1.50 g, 3.42 mmol) in ethyl acetate (50 mL) at 0°C was bubbled HCl until it was saturated. The reaction mixture was stirred for one hour and evaporated to yield the salt (1.32 g, 100%).
¹H NMR (CD₃OD, 400MHz) δ 7.40-7.18 (m, 10 H), 5.14 (s, 2 H), 3.43, 3.42 (2 d, J = 14.8 Hz, 1 H), 3.23 (td, J = 4 Hz, 12.1 Hz, 1 H), 3.00 (d, J = 13 Hz, 1 H), 2.94 (d, J = 14.7 Hz, 1 H), 2.83 (dt, J = 3.4 Hz, 12 Hz, 1 H), 2.74 (d, J = 13 Hz, 1 H), 2.68 (d, J = 13.6 Hz, 1 H), 2.62 (d, J = 13.6 Hz, 1 H), 2.00-1.90 (m, 1 H), 1.92-1.88 (m, 1 H), 1.59-1.52 (m, 1 H), 1.47-1.44 (m, 1H).
FAB-MS calc. for C₂₁H₂₆N₂O₂: 338; Found 339 (M+H)

- 316 -

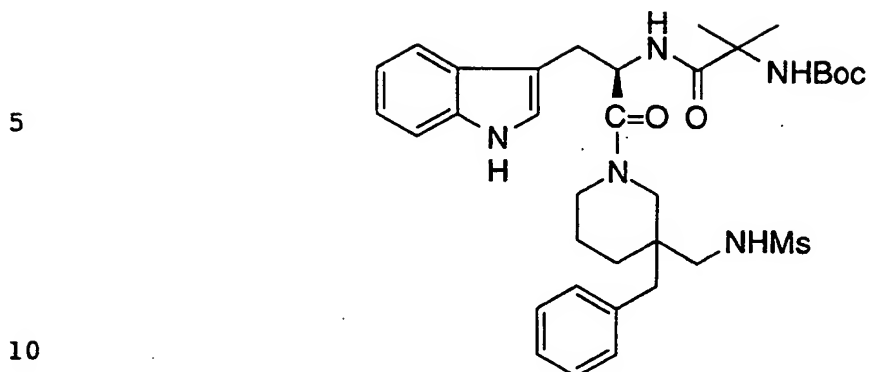
Step F:

Prepared by the procedure described in Example C1, Step D from the intermediate prepared in the previous step (1.00 g, 2.67 mmol), Intermediate 1 (1.04 g, 1 eq.), HOBT (1 eq.), N-methyl morpholine (2 eq.), and EDC (820 mg, 4.27 mmol). Purification by MPLC, eluting with 60% ethyl acetate in hexane, provided the compound. (1.54 g, 81%)

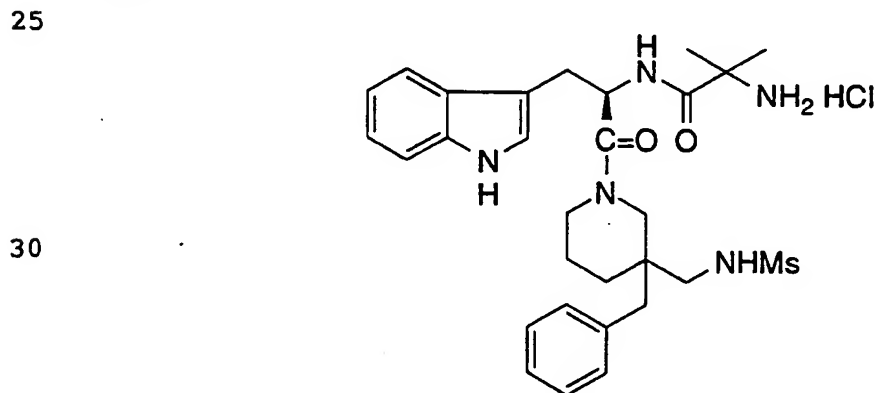
Step G:

The intermediate from the previous step (1.30 g, 1.83 mmol) was hydrogenated over 10% palladium on carbon (100 mg) in ethanol (15 mL) under a hydrogen balloon. The reaction mixture was filtered through celite and evaporated to yield the amine (1.20 g, 100%). FAB-MS calc. for C₃₃H₄₅N₅O₄: 575; Found 576 (M+H)

- 317 -

Step H:

To a stirred solution of the intermediate prepared the previous step (286 mg, 0.497 mmol), DMAP (10 mg) and N-methyl morpholine (0.109 mL) in dichloromethane (10 mL) at 0°C was added
15 mesyl chloride (0.042 mL). The reaction mixture was stirred for 2 hours. The solution was poured into a mixture of brine and 3 N HCl and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate dried over magnesium sulfate and evaporated to give a residue which was purified by flash
20 chromatography, eluting with 90% ethyl acetate in hexane, to give the product (285.9 mg, 88%). FAB-MS calc. for C₃₄H₄₇N₅O₆S: 653; Found 654 (M+H)

Step I:

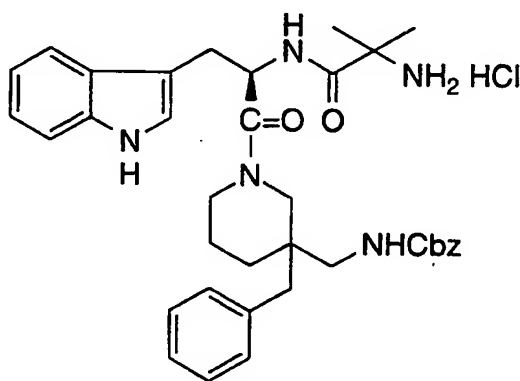
- 318 -

Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (265 mg, 0.405 mmol) and HCl gas in ethyl acetate (8 mL) at 0°C for 30 minutes (189 mg, 79%)
FAB-MS calc. for C₂₉H₃₉N₅O₄S: 553; Found 554 (M+H)

5

EXAMPLE C20

10



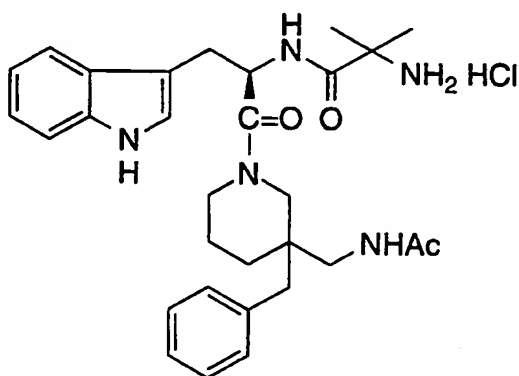
15

Prepared by the procedure described in Example C1, Step C from the intermediate from Example C19, Step F (109 mg, 0.154 mmol) and HCl gas in ethyl acetate (4 mL) at 0°C for 30 minutes (90 mg, 90%).
FAB-MS calc. for C₃₆H₄₃N₅O₄: 609; Found 610 (M+H)

20

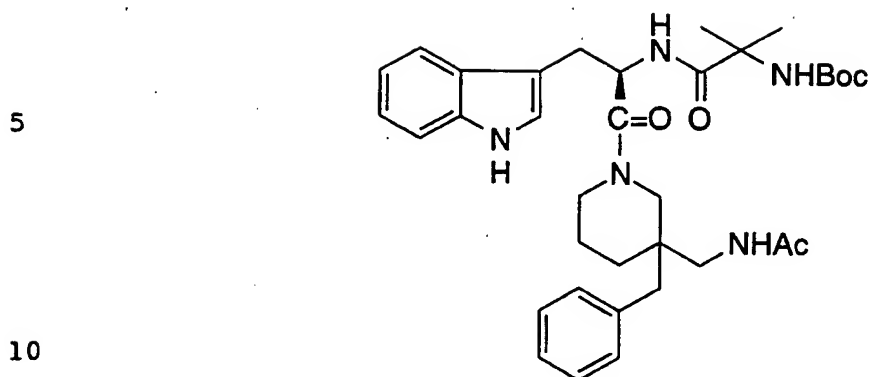
EXAMPLE C21

25



30

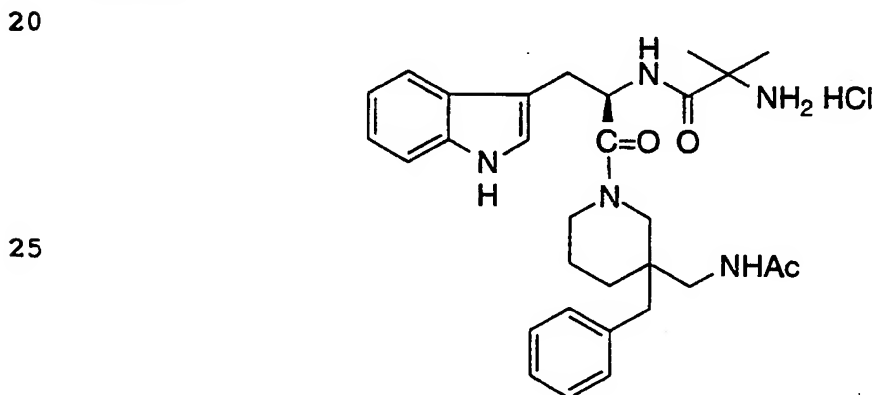
- 319 -

Step A:

The mixture of the intermediates from Example C19, Step G (208 mg, 0.362 mmol) and pyridine (2 mL) and acetic anhydride (2 mL) was heated at 60°C for 30 minutes. The mixture was then evaporated under vacuum. MPLC purification eluting with 80% ethyl acetate in hexane yielded the product (202 mg, 90%).

15

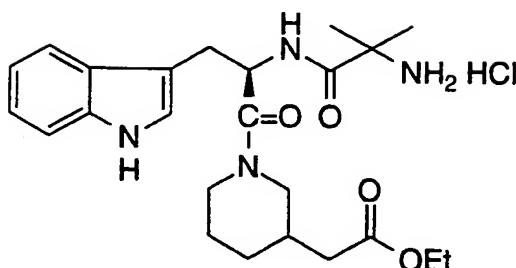
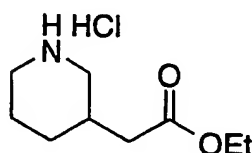
FAB-MS calc. for C₃₅H₄₇N₅O₅: 617; Found 618 (M+H)

Step B:

Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (192 mg, 0.311 mmol) and HCl gas in ethyl acetate (4 mL) at 0°C for 30 minutes (168.1 mg, 98.5%).

FAB-MS calc. for C₃₀H₃₉N₅O₃: 517; Found 518 (M+H)

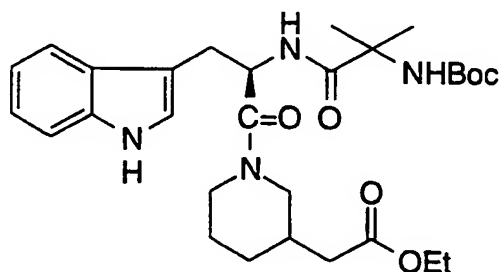
- 320 -

EXAMPLE C22Step A:

A suspension of platinum (IV) oxide (200 mg), ethyl 3-pyridylacetate (5.0 g, 30.3 mmol) and concentrated hydrochloric acid (10 mL) in ethanol (50 mL) was stirred under a hydrogen balloon overnight. The mixture was filtered through celite and evaporated to yield a residue, which was refluxed with anhydrous acidic ethanol for 30 minutes.

Evaporation yielded the product (6.28 g, 100%).

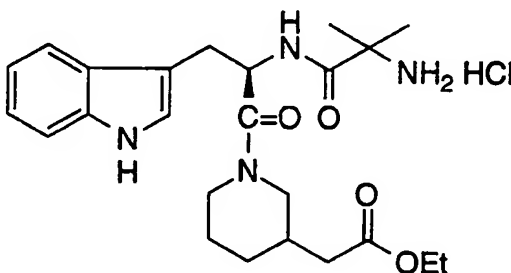
^1H NMR (CD_3OD , 400MHz) δ 4.13 (q, $J = 7.2$ Hz, 2 H), 3.40 (dd, $J = 3.5$ Hz, 12 Hz, 1 H), 3.35 (br. d, 1 H), 2.90 (br. t, 1 H), 2.73 (t, $J = 12$ Hz, 1 H), 2.35 (d, $J = 7.5$ Hz, 2 H), 2.26-2.17 (m 1 H), 1.96-1.80 (br. m, 2 H), 1.80-1.70 (m, 1 H), 1.37-1.26 (m, 1 H), 1.24 (t, $J = 7.1$ Hz, 3H).

Step B:

- 321 -

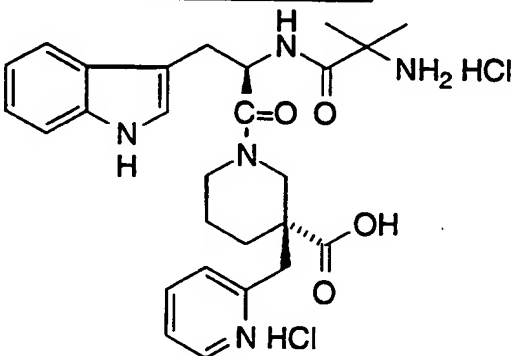
Prepared by the procedure described in Example C1, Step D from the intermediate prepared in the previous step (128 mg, 0.617 mmol), Intermediate 1 (200 mg, 0.514 mmol), HOBT (1 eq.), N-methyl morpholine (1 eq.), and EDC (200 mg). Purification by MPLC eluting with 80% ethyl acetate in hexane provided the compound. (247 mg, 89%)

Step C:

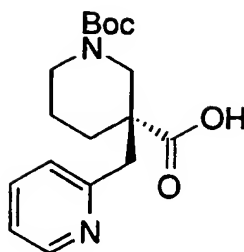


Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (225 mg, 0.415 mmol) and HCl gas in ethyl acetate (5 mL) at 0°C for 15 minutes (184 mg, 100%). FAB-MS calc. for C₂₄H₃₄N₄O₄: 442; Found 443 (M+H)

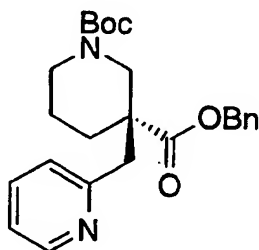
EXAMPLE C23



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Step A:

10 The less polar (d1) intermediate from Example C8 step A (7.25g, 17.08 mmol) was refluxed for 8 hours in ethanol (20 ml) and 10N NaOH (8.5 mL). The mixture was then cooled to room temperature and slowly treated with 3 N HCl to pH=11. To this stirred solution was added di-tert-butyl dicarbonate in dioxane (20 mL) and stirred for two hours. The solution was acidified to pH 4 and then neutralized to pH 7 and extracted with ethyl acetate three times. The organic extracts were combined, dried, and concentrated to give white solid (6.80g). FAB-MS calc. for C₁₇H₂₄N₂O₄: 320, Found: 321 (M+H)

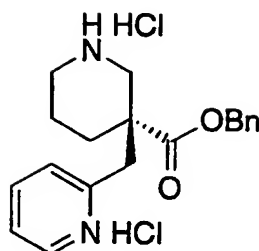
Step B:

30 To a solution of the intermediate from the last step (6.5 g), benzyl alcohol (2 equiv.), and DMAP (20 mg) in dichloromethane (100 mL), was added EDC (1.2 equiv.). The mixture was stirred at room temperature for three days, and was poured into dilute NaHCO₃ solution. It was extracted with ethyl acetate three times, and dried over MgSO₄. Evaporation and purification by a flash column eluting with 40% ethyl acetate in hexane gave the desired product.(6.53 g, 78%). FAB-MS calc. for C₂₄H₃₀N₂O₄: 410 ; Found 411 (M+H); 311 (M+-Boc(100)) .

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Step C:

5



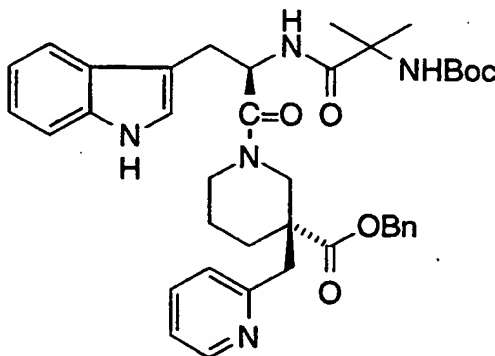
10

Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (1.0 g, 2.44 mmol) in ethyl acetate (40 mL) and HCl gas at 0°C for 15 minutes (935 mg, 99%). FAB-MS calc. for C₁₉H₂₂N₂O₂: 310 ; Found 311 (M+H)

Step D:

15

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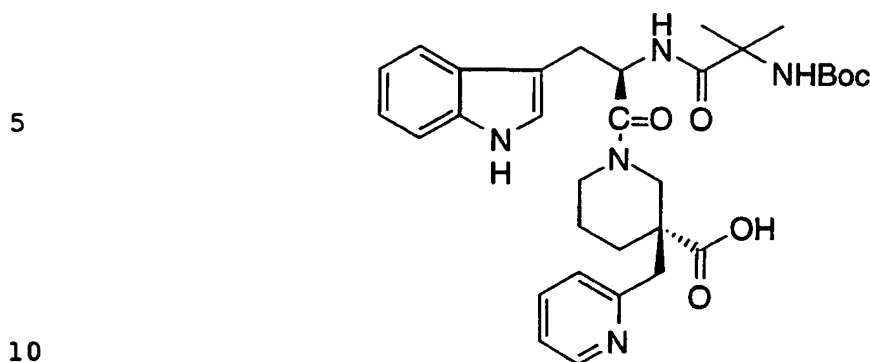


25

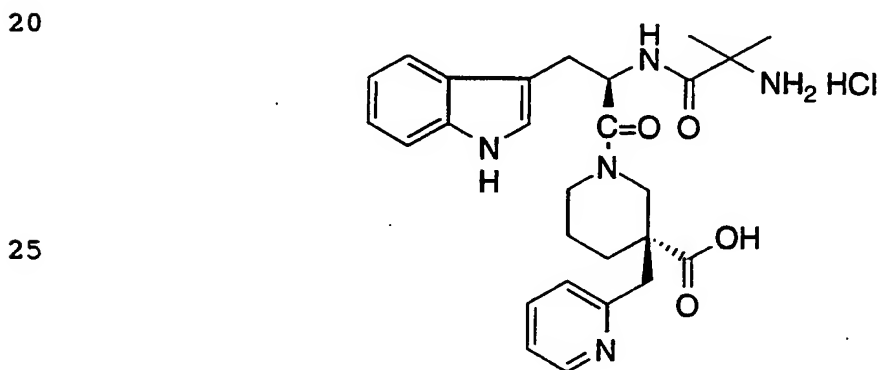
30

Prepared by the procedure described in Example C1, Step D from the intermediate prepared in the previous step (800 mg, 2.09 mmol), intermediate 1 (812 mg, 2.09 mmol), HOBT (1 eq.), N-methyl morpholine (1 eq.), and EDC (2 eq.). Purification by MPLC, eluting with 80% ethyl acetate in hexane, provided the Intermediate (1.10g, 77%) d1 FAB-MS calc. for C₃₉H₄₇N₅O₆: 681; Found 682 (M+H)

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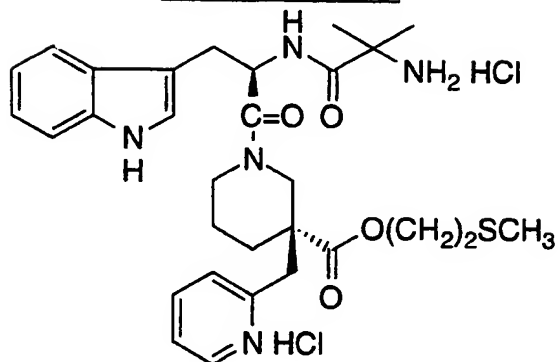
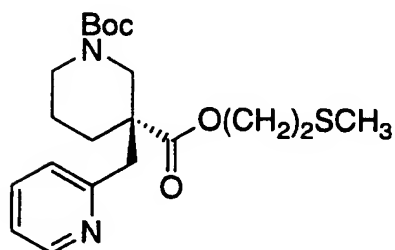
Step E:

A suspension of 10% palladium on carbon (150 mg) and the intermediate from previous step (1.05 g, 1.54 mmol) in ethanol (20 mL) was vigorously stirred under a hydrogen atmosphere for 30 minutes. The reaction mixture was then filtered through celite and evaporated to give the product (828 mg, 91%). d1 FAB-MS calc. for $C_{32}H_{41}N_5O_6$: 591 ; Found 592 (M+H)

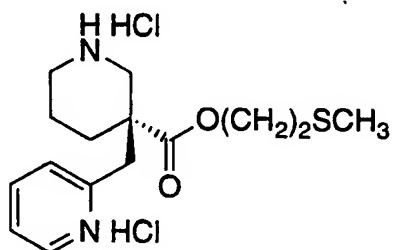
Step F:

Prepared by the procedure described in Example C1; Step C from the intermediate from the previous step (211 mg, 0.357 mmol) and HCl gas in ethyl acetate (15 mL) at 0°C for 10 minutes (175.6 mg, 93%). d1 FAB-MS calc. for $C_{27}H_{33}N_5O_4$: 491 Found 492 (M+H)

- 325 -

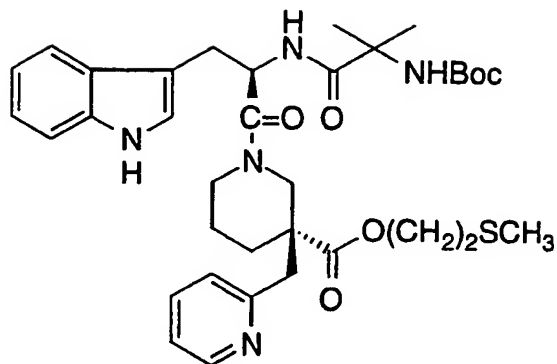
EXAMPLE C24Step A:

To a stirred solution of the product from Example C23, step A (5.79 g, 18.1 mmol), 2-(methylthio)ethanol (2.49 g, 27.1 mmol), DMAP (220 mg) in dichloromethane (100 mL) was added EDC and the mixture was stirred for one day. The reaction mixture was washed with brine, dried, evaporated, and purified on silica gel column eluting with 60% ethyl acetate in hexane to give the desired compound (6.64 g, 94%) FAB-MS calc. for C₂₀H₃₀N₂O₄S: 394, Found: 395 (M+H)

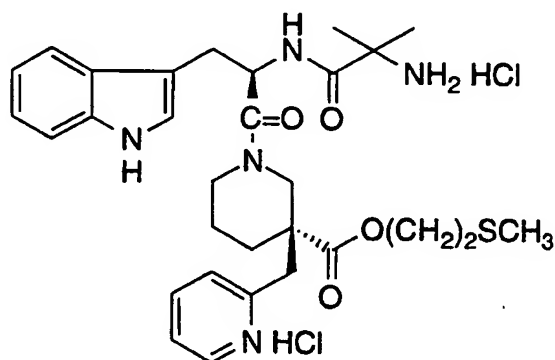
Step B:

Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (6.12 g, 15.5 mmol) in ethyl acetate (30 mL) and HCl gas at 0°C for 30 minutes (5.38 g, 95%). FAB-MS calc. for C₁₅H₂₂N₂O₂S: 294 ; Found 295 (M+H)

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Step C:

Prepared by the procedure described in Example C1, Step D from the intermediate prepared in the previous step (2.0 g, 5.44 mmol), Intermediate 1 (2.12, 5.44 mmol), HOBT (1 eq.), N-methyl morpholine (1 eq.), and EDC (1.5 eq.). Purification by MPLC, eluting with 80-100% ethyl acetate in hexane, provided the intermediate (3.44g, 95%)
 FAB-MS calc. for C₃₅H₄₇N₅O₆S: 665 ; Found 666(M+H)

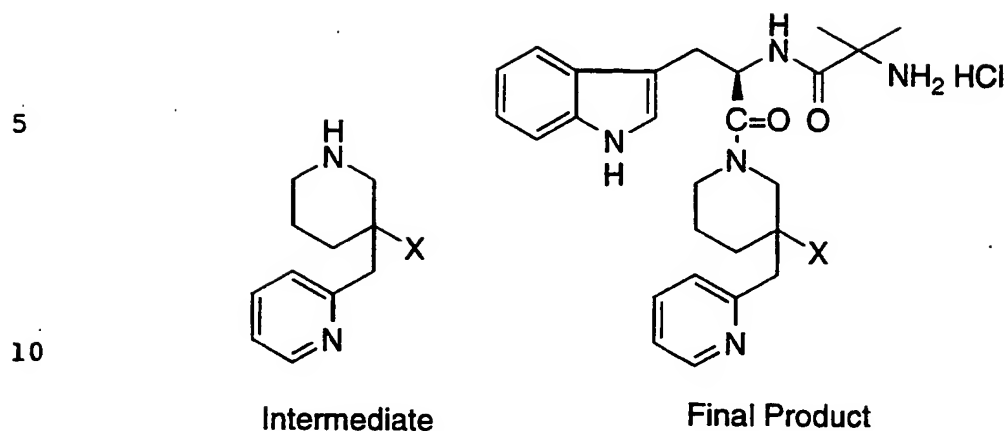
Step D:

Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (2.94 g, 4.42 mmol) in ethyl acetate (10 mL) and HCl gas at 0°C for 20 minutes (2.80 g, 99%).
 FAB-MS calc. for C₃₀H₃₉N₅O₄S: 565 ; Found 566(M+H)

The additional intermediates shown in Table CVII were prepared according to the above established procedure as exemplified in Example C24, steps A and B,. The final compounds were prepared according to Example C17 Steps D and E, using Intermediate 1.

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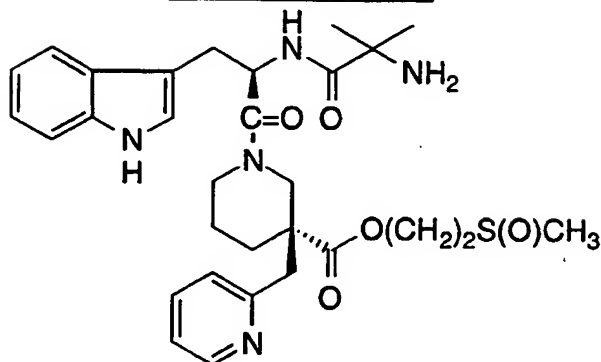
TABLE CVII



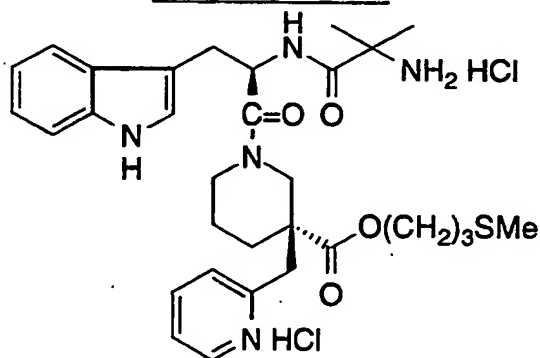
| | entry | X | Intermediate MF FAB-MS(M+1) | Final Product MF FAB-MS(M+1) | isomer |
|----|-------|---|--|--|--------|
| 15 | | | | | |
| | 1 | CO ₂ (CH ₂) ₂ SMe | C ₁₅ H ₂₂ N ₂ O ₂ S 295 | C ₃₀ H ₃₉ N ₅ O ₄ S 566 | R |
| | 2 | CO ₂ Bn | C ₁₉ H ₂₂ N ₂ O ₂ 311 | C ₃₄ H ₃₉ N ₅ O ₄ 582 | R |
| | 3 | CO ₂ Bn | C ₁₉ H ₂₂ N ₂ O ₂ 311 | C ₃₄ H ₃₉ N ₅ O ₄ 582 | S |
| 20 | 4 | CO ₂ (CH ₂) ₃ CH ₃ | C ₁₆ H ₂₄ N ₂ O ₂ 277 | C ₃₁ H ₄₁ N ₅ O ₄ 548 | RS |
| | 5 | CO ₂ (CH ₂) ₂ CH ₃ | C ₁₅ H ₂₂ N ₂ O ₂ 263 | C ₃₀ H ₃₉ N ₅ O ₄ 534 | RS |
| | 6 | CO ₂ CH(CH ₃) ₂ | C ₁₅ H ₂₂ N ₂ O ₂ 263 | C ₃₀ H ₃₉ N ₅ O ₄ 534 | RS |
| | 7 | CONH(CH ₂) ₃ CH ₃ | C ₁₆ H ₂₅ N ₃ O 276 | C ₃₁ H ₄₂ N ₆ O ₃ 547 | RS |
| 25 | 8 | CONHCH(CH ₃) ₂ | C ₁₅ H ₂₃ N ₃ O 262 | C ₃₀ H ₄₀ N ₆ O ₃ 533 | RS |
| | 9 | CO ₂ CH ₂ CO ₂ Et | C ₁₆ H ₂₂ N ₂ O ₄ 306 | C ₃₁ H ₃₉ N ₅ O ₆ 578 | RS |
| | 10 | CONHEt | C ₁₄ H ₂₁ N ₃ O 248 | C ₂₉ H ₃₈ N ₆ O ₃ 519 | RS |
| 30 | 11 | CONHCH ₂ CO ₂ Et | C ₁₆ H ₂₃ N ₃ O ₃ 307 | C ₃₁ H ₄₀ N ₆ O ₅ 577 | RS |

Note: RS compounds were prepared by using racemic intermediates instead of chiral ones.

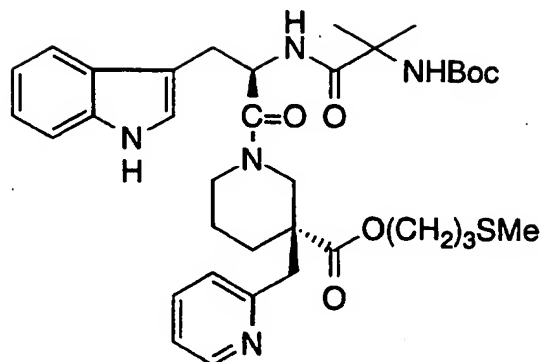
- 328 -

EXAMPLE C24A

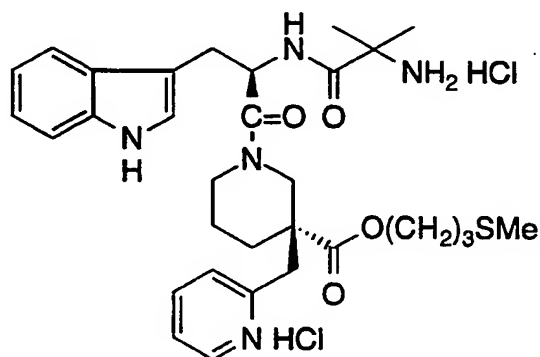
To a stirred solution of the final product from Example C24 (120 mg, 0.188 mmol) in ethanol/water (3/2 mL), was added sodium periodate (100 mg, 0.467 mmol) and the resulting mixture was stirred at room temperature for six hours. The reaction mixture was then poured into saturated sodium bicarbonate solution (10 mL) and extracted with dichloromethane (10 mL, 3 times). The organic extracts were combined and evaporated to give the desired compound (89 mg, 81%).
FAB-MS calc. for C₃₀H₃₉N₅O₅S: 581 ; Found 582(M+H)

EXAMPLE C25

- 329 -

Step A:

To a stirred solution of the intermediate from Example C23, step E (100 mg, 0.17 mmol), 3-(methylthio) propanol (18 mg, 0.17 mmol) and DMAP (3 mg) in dichloromethane (15 mL) was added EDC (1.5 equiv.), and the mixture was stirred at room temperature for one day. The reaction mixture was washed with water and brine, dried, evaporated and purified by MPLC eluting with 80% ethyl acetate in hexane to give the desired compound (88 mg). FAB-MS calc. for $C_{36}H_{49}N_5O_6S$: 679 ; Found 680(M+H)

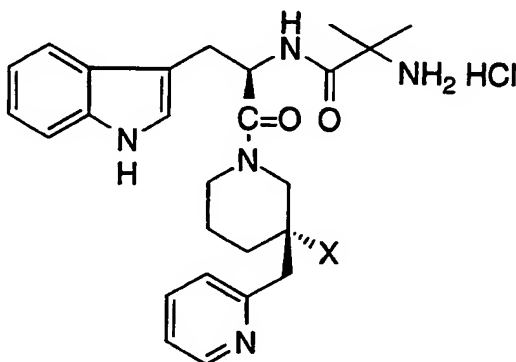
Step B:

Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (85 mg, 0.125 mmol) in ethyl acetate (3 mL) and HCl gas at 0°C for 20 minutes (74 mg, 95%). FAB-MS calc. for $C_{31}H_{41}N_5O_4S$: 579 ; Found 580(M+H)

- 330 -

The compounds shown in Table CVIII were prepared according to the above established procedure as exemplified in Example C25 using appropriate amines and alcohols.

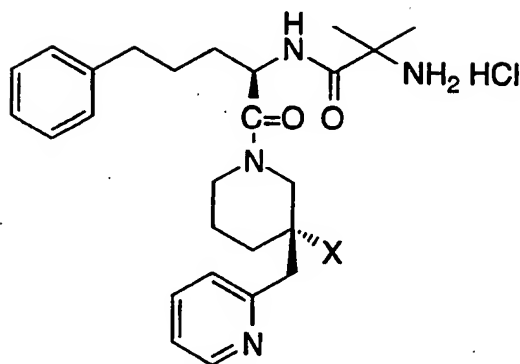
TABLE CVIII



| entry | X | MF FAB-MS(M+1) |
|-------|---|---|
| 1 | CO(morpholine) | C ₃₁ H ₄₀ N ₆ O ₄ 560 (M ⁺ , EI MS) |
| 2 | CO ₂ (CH ₂) ₄ SMe | C ₃₂ H ₄₃ N ₅ O ₄ S 594 |
| 3 | CONH(CH ₂) ₂ SMe | C ₃₀ H ₄₀ N ₆ O ₃ S 565 |
| 4 | CONHEt | C ₂₉ H ₃₈ N ₆ O ₃ 519 |
| 5 | CONH(CH ₂) ₂ OH | C ₂₉ H ₃₈ N ₆ O ₄ 535 |

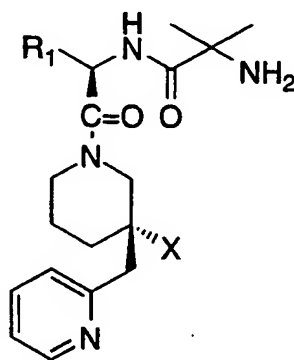
Likewise using the intermediate from Example C23, Step C and following the procedures described in Step D and E using Intermediate 3 instead of Intermediate 1, the compounds shown in Table CVIIIa were prepared according to the established procedures as exemplified in Example C25 using appropriate amines.

- 331 -

TABLE CVIIIa

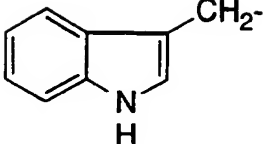
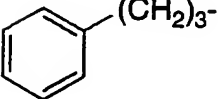
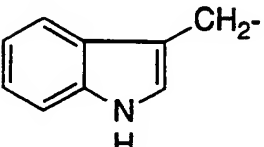
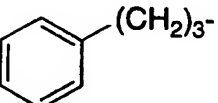
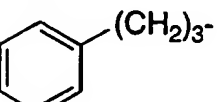
| entry | X | MF FAB-MS(M+1) |
|-------|--|--|
| 1 | CONHEt | C ₂₉ H ₄₁ N ₅ O ₃ 508 |
| 2 | CONH(CH ₂) ₂ OH | C ₂₉ H ₄₁ N ₅ O ₄ 524 |

Likewise using the intermediate from Example C23, Step E and following the procedure described above; or the intermediate from Example C23, step A and following the procedure described in Example C24 steps A through D using Intermediate 1 or Intermediate 3 the compounds shown in Table CVIIIb may be prepared.

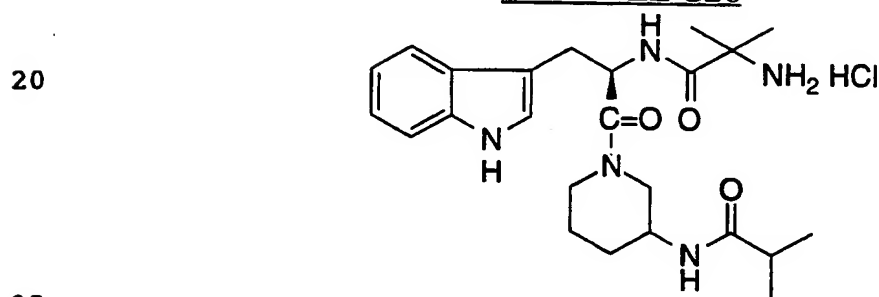
TABLE CVIIIb

| entry | R1 | X |
|-------|----|---|
|-------|----|---|

- 332 -

- | | | |
|---|---|---|
| 1 |  | -CONHCl ₃ |
| 2 |  | -CONHCH ₃ |
| 3 |  | -CONH(CH ₂) ₃ OH |
| 4 |  | -CONH(CH ₂) ₃ OH |
| 5 |  | -CONHCH ₂ CH ₂ SCH ₃ |

EXAMPLE C26



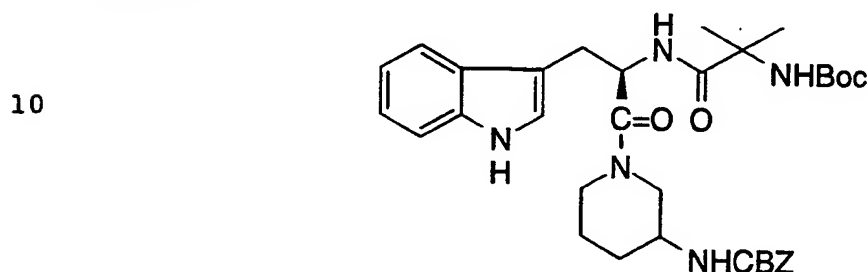
Step A: **3-Carbobenzyloxyaminopyridine**

To a solution of 3-aminopyridine (10 g, 0.106 mol) and triethyl amine (16.3 mL, 0.117 mol) in dichloromethane (100 mL) at 0°C, was added benzyl chloroformate (15.2 mL, 0.106 mol) slowly. The reaction mixture was stirred overnight and was washed with water, saturated NaHCO₃, dried over MgSO₄, and evaporated. The residue was purified on a silica gel column to give the product (9.51 g) FAB-MS calc. for C₁₃H₁₂N₂O₂: 228 ; Found 229(M+H)

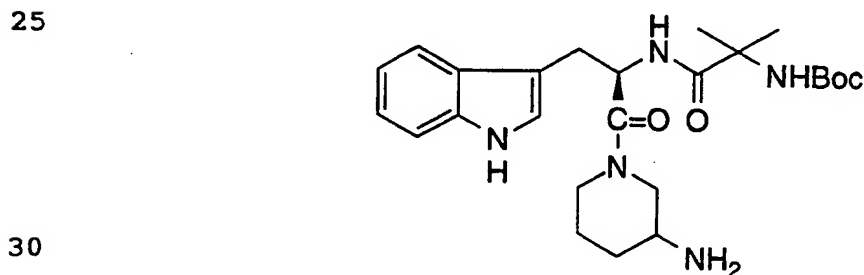
Step B: **3-Carbobenzyloxyaminopiperidine**

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A solution of the intermediate from the previous step (9.51 g, 41.7 mmol) and hydrochloric acid (3.5 mL, 41.7 mmol) in ethanol (300 mL) was hydrogenated over PtO₂ (0.9 g) and hydrogen (1 atm) overnight. Filtration and evaporation gave the product as a brown solid.
 5 FAB-MS calc. for C₁₃H₁₈N₂O₂: 234 ; Found 235(M+H)

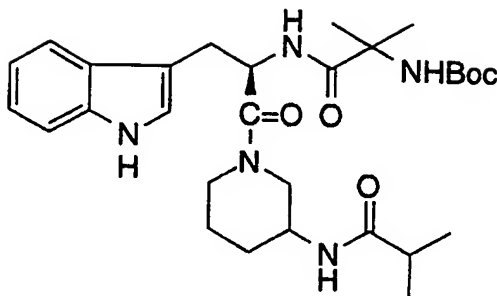
Step C:

To a solution of the intermediate from the previous step (4.65 g, 17.2 mmol), Intermediate 1 (6.68 g, equiv.), HOBT (2.32 g, 1 equiv.) and NMM (2.1 mL, 1 equiv.) in dichloromethane (100 mL), was added EDC (3.94 g, 1.2 equiv.). The reaction mixture was stirred overnight and worked up by washing with water, saturated NaHCO₃, dried over MgSO₄ and evaporated. Purification on a SiO₂ column gave
 20 2.5 g of the desired product.
 FAB-MS calc. for C₃₃H₄₃N₅O₆: 605 ; Found 606(M+H)

Step D:

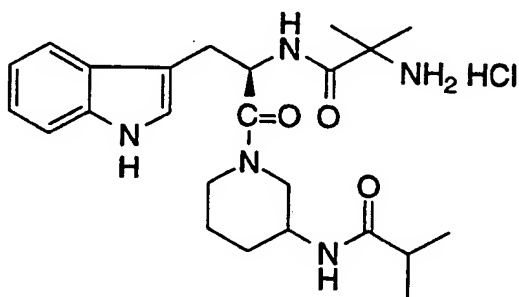
A suspension of the intermediate from the previous step (2.5 g) and Pd(OH)₂/C (250 mg, 10 %) in methanol (60 mL) was stirred under H₂ (1 atm) for three days. The reaction mixture was filtered through celite and evaporated to give the desired material.
 FAB-MS calc. for C₂₅H₃₇N₅O₄: 471 ; Found 472(M+H)

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Step E:

To a solution of the intermediate from the previous step (236 mg, 0.5 mmol) and N,N-diisopropylethylamine (0.11 mL, 0.6 mmol) in dichloromethane (10 mL), was added isobutyryl chloride (0.053 mL, 0.5 mmol) at 0°. The reaction mixture was stirred for 2 hours and was washed with water, brine, dried over MgSO₄ and evaporated. SiO₂ flash column chromatography eluting with 90-100% ethyl acetate in hexane yielded the product.

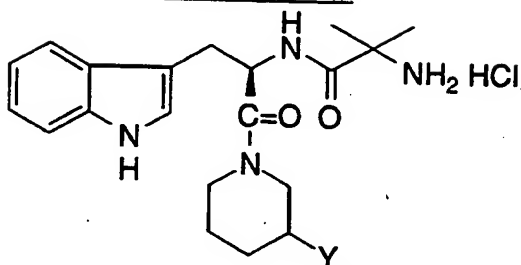
FAB-MS calc. for C₂₉H₄₃N₅O₅: 541 ; Found 542(M+H)

Step F:

To a solution of the intermediate from the previous step in ethyl acetate (5 mL) at 0°C was bubbled HCl until it was saturated. The mixture was stirred for 30 minutes and evaporated to dryness to give the product. FAB-MS calc. for C₂₄H₃₅N₅O₃: 441 ; Found 442(M+H)

Similarly the following compounds were prepared according to the same procedure as described above, but using different acylating reagents.

- 335 -

TABLE CIX

5

10

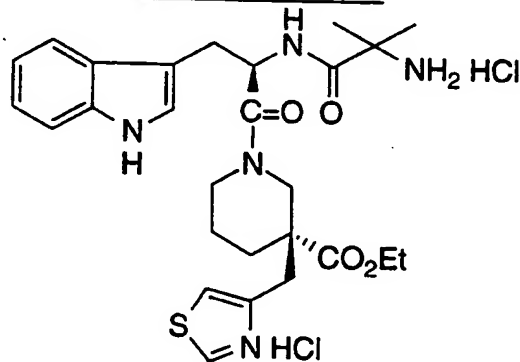
15

20

| entry | Acylating agent | Y | MF FAB-MS(M+1) |
|-------|-------------------------|-------------------------|--|
| 1 | Ac ₂ O | AcNH | C ₂₂ H ₃₁ N ₅ O ₃ 414 |
| 2 | ChxCOCl | ChxCONH | C ₂₇ H ₃₉ N ₅ O ₃ 482 |
| 3 | ChxCH ₂ COCl | ChxCH ₂ CONH | C ₂₈ H ₄₁ N ₅ O ₃ 496 |
| 4 | BzCl | BzNH | C ₂₇ H ₃₃ N ₅ O ₃ 476 |
| 5 | PhSO ₂ Cl | PhSO ₂ NH | C ₂₆ H ₃₃ N ₅ O ₄ S 512 |
| 6 | iso-PrNCO | iso-PrNHCONH | C ₂₄ H ₃₆ N ₆ O ₃ 457 |

note: Chx: cyclohexyl, Bz: benzoyl

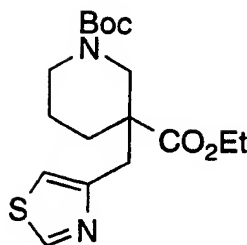
25

EXAMPLE C27

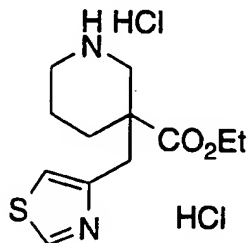
30

Step A:

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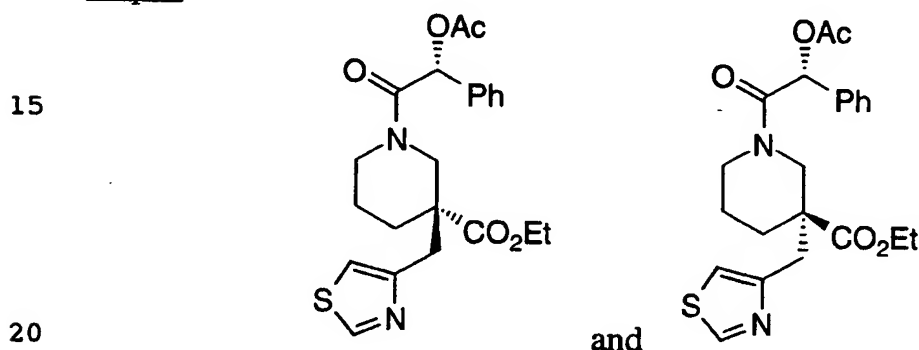


5 To a stirred solution of KHMDS (27.4 g, 0.138 mol) in THF (500 mL) at -78°C under argon was added ethyl N-t-Boc nipecotate (28.3 g, 0.11 mol) in THF (100 mL) over a 20 minute period. The solution was
10 allowed to stir an additional 30 minutes at -78°C. Then, a solution of 4-bromomethylthiazole or 4-chloromethylthiazole in THF (100 mL) was added slowly to the reaction mixture. 4-Bromomethylthiazole was prepared by refluxing 4-methylthiazole (10 mL, 0.11 mmol), N-bromosuccinimide (19.6 g, 0.11 mol) and AIBN (0.2 g) in CCl₄ (300
15 mL) for 2 hours, cooled to room temperature, filtered and evaporated; 4-chloromethylthiazole can be prepared as described by Hsiao, C-H et al, Synthetic Communications, 20 (22), 3507-3417 (1990) and Caldwell, W and Fox, S.M. J. Am. Chem. Soc. 73, 2935 (1955). The resulting black mixture was stirred overnight and allowed to warm to room temperature.
20 The material was concentrated, then diluted with water, and extracted using ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by silica gel flash column chromatography eluting with a solvent gradient of 30-65% ethyl acetate in hexane provided the title compound. (7.58 g, 20%).
25 FAB-MS calc. for C₁₇H₂₆N₂O₄S 354; Found 355 (M+H)

Step B:

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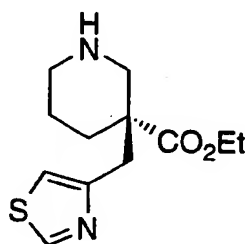
To a solution of the intermediate from the previous step (7.0 g, 19.8 mmol) in ethyl acetate (100 mL) at 0°C, was bubbled hydrogen chloride gas until saturation occurred. The reaction was stirred for 30 minutes, and then concentrated to remove the ethyl acetate to afford the product (5.3g, 93%). ¹H NMR (CDCl₃, 400MHz) δ 9.67 (s, 1 H), 7.75 (s, 1 H), 4.34-4.15 (2 m, 2 H), 3.67 (d, J=12.8 Hz, 1 H), 3.34 (d, J=15 Hz, 1 H), 3.28 (d, J=12.5 Hz, 1 H), 3.21 (d, J=15 Hz, 1 H), 3.01 (dt, J=3.0, 12.5 Hz, 1 H), 2.26 (br. d, J=13.7 Hz, 1 H), 1.97-1.92 (m, 1 H), 1.80 (dt, J=3.5, 13 Hz, 1 H), 1.78-1.58 (m, 1 H), 1.26 (t, J=7.2 Hz, 3 H). FAB-MS calc. for C₁₂H₁₈N₂O₂S: 254 ; Found 255 (M+H)

Step C:

To a stirred solution of the intermediate (6g, 18.67 mmol) prepared in Step B, (R)-(-)-(O)-acetyl mandelic acid (1 eq.), HOBT (1 eq.) and NMM (2 eq.) at 0°C was added EDC (7.16g, 37.34 mmol). The reaction mixture was stirred overnight during which time it was allowed to warm to room temperature. The solution was poured into brine and extracted with CH₂Cl₂. The organic layer was dried over MgSO₄, evaporated and purified with a SiO₂ flash column eluting with 40-80% ethyl acetate in hexane to provided two enantiomerically pure compounds. The isomer which came out of the column first was designated as d1 (2.17 g, 30%) and the isomer which came out of the column second as d2 (0.87 g, 12%) and mixed fractions (700 mg). The initial stereochemistry assignment was made by NMR comparison of these compounds with the intermediates obtained in Example C8 Step A. The absolute stereochemistry of those intermediates was established by X-ray analysis. The assignment was later confirmed by an X-ray analysis

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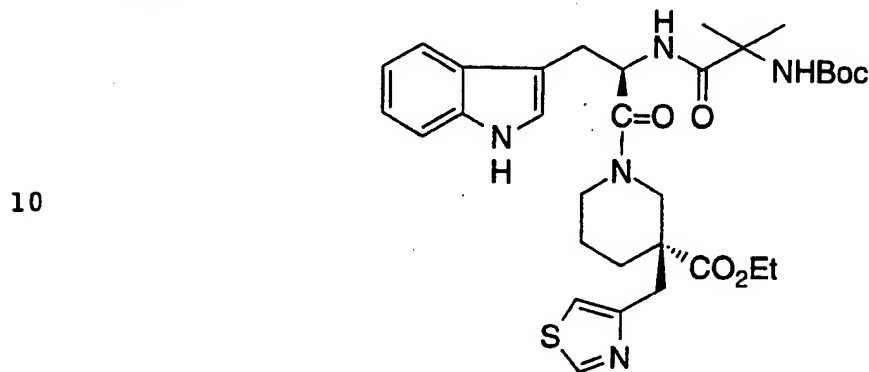
of Intermediate 1. FAB-MS calc. for $C_{22}H_{26}N_2O_5S$: 430 ; Found 431(M+H) d1: 1H NMR ($CDCl_3$, 400MHz) indicated the compound exists as a mixture of two conformers. δ 8.77, 8.65 (2 s, 1 H), 7.46-7.34 (m, 5 H), 7.07, 7.02 (2 s, 1 H), 6.64, 6.23 (2s, 1 H), 4.29 (br. d, J=13.9 Hz, 1/2 H), 4.10-4.02 (m, 3/2 H), 3.92-3.87 (m, 3/2 H), 3.61 (d, J=13.5 Hz, 1/2 H), 3.46 (d, J=14 Hz, 1/2 H), 3.40-3.32 (m, 1/2 H), 3.25-3.21 (m, 1/2 H), 3.18 (d, J=14 Hz, 1/2 H), 3.06 (d, J=14 Hz, 1/2 H), 2.96 (d, J=14 Hz, 1/2 H), 2.84 (d, J=14 Hz, 1/2 H), 2.85-2.75 (br. m, 1/2 H), 2.14, 2.11 (2s, 3 H), 1.90-1.82 (m, 1 1/2 H), 1.80-1.75 (m, 1 H), 1.61-1.55 (m, 1 H), 1.50-1.40 (br. m, 1/2 H), 1.14 (t, J= 7 Hz, 3/2 H), 1.03 (t, J= 7 Hz, 3/2 H). d2: 1H NMR ($CDCl_3$, 400MHz) indicated the compound exists as a mixture of two conformers. δ 8.71, 8.68 (2d, J=1.8 Hz, 1 H), 7.41-7.34 (m, 5 H), 7.06, 6.83 (2 d, J=1.8 Hz, 1 H), 6.41 6.20 (2s, 1 H), 4.46 (br. d, J=13.4 Hz, 1/2 H), 4.24-3.93 (m, 3 H), 3.41 (d, J=13.5 Hz, 1/2 H), 3.31-3.28 m, 1 H), 3.13 (d, J=14.2 Hz, 1/2 H), 3.04 (d, J=14.2 Hz, 1/2 H), 3.04 (d, J=14.2 Hz, 1/2 H), 2.92 (d, J=14 Hz, 1/2 H), 2.73 (d, J=14 Hz, 1/2 H), 2.54 (d, J=13.8 Hz, 1 H), 2.30 (br. d, J=13 Hz), 2.15, 2.09 (2 s, 3 H), 2.00-1.95 (m, 1/2 H), 1.65-1.49 (m, 2 H), 1.37 (dt, J=4, 12.8 Hz, 1/2 H), 1.17-1.10 (m, 3 H).

Step D:

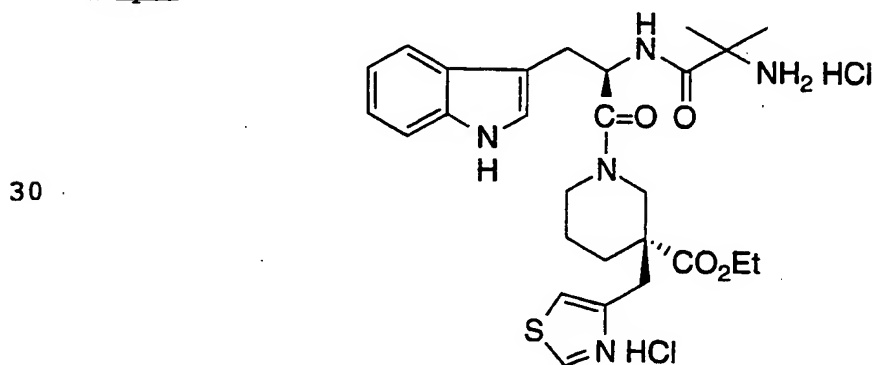
A solution of the intermediate d1 from the previous step (2.0 g, 4.65 mmol) concentrated hydrochloric acid (25 mL) and ethanol (25 mL) was refluxed for 3 hours and was evaporated to dryness. The residue was neutralized by ammonium hydroxide and extracted by dichloromethane, and then was purified by SiO₂ flash column eluting with 1:10:90 NH₄OH:MeOH:CHCl₃ to yield the product (0.72 g, 61%). 1H NMR (CD_3OD , 400MHz) δ 8.88 (d, J=2 Hz, 1 H), 7.21 (d, J=2 Hz, 1 H), 4.20-4.07 (m, 2 H), 3.28 (br. d, 1 H), 3.06 (d, JAB=14 Hz, 1 H), 2.97

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(d, JBA=14 Hz, 1 H), 2.92-2.80 (md, 1 H), 2.61-2.57 (m, 2 H), 2.21-2.16 (br. d, 1 H), 1.66-1.40 (m, 3 H), 1.20 (t, J=7.3 Hz, 3 H).
FAB-MS calc. for C₁₂H₁₈N₂O₂S : 254 ; Found 255 (M+H)

5 Step E:

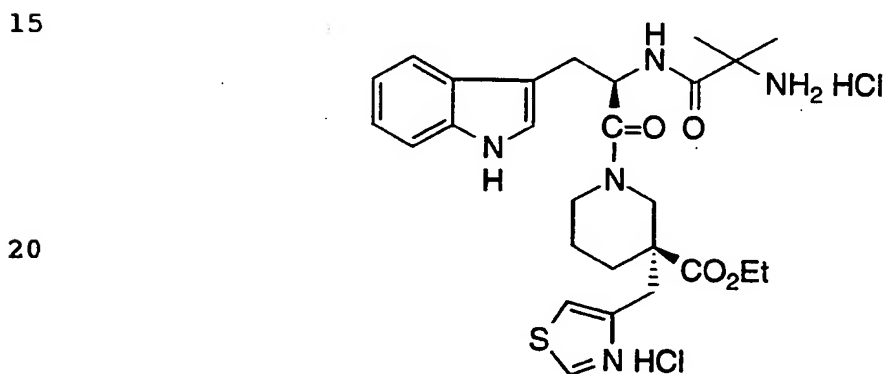
15 To a stirred solution of the intermediate from the previous step (163 mg, 0.642 mmol), Intermediate 1 (250 mg, 0.642 mmol) and HOBT (87 mg, 0.642 mmol) in dichloromethane (20 mL) was added EDC (247 mg, 1.28 mmol) at 0°C. The reaction mixture was stirred overnight and allowed to warm to room temperature. The solution was
20 washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 60% ethyl acetate in hexane provided the desired compound (285 mg, 71%). FAB-MS calc. for C₃₂H₄₃N₅O₆S : 625 ; Found 626 (M+H); 526 (M⁺-Boc(100)).

25 Step F:

- 340 -

Hydrogen chloride gas was bubbled into a solution of the intermediate from the previous step (270 mg, 0.43 mmol) in ethyl acetate (10 mL) at 0°C until it was saturated. The reaction was stirred for 30 minutes, and evaporated to remove the ethyl acetate to afford the product (226 mg, 93%). ¹H NMR (CD₃OD, 400MHz): 9.90 (d, J=2.2Hz, 4/5H), 9.5 (d, J=2.2 Hz, 1/5H), 8.48 (d, J=7.15, 4/5H), 8.15 (d, 7.15, 1/5H), 7.70 (d, J=2.2 Hz, 4/5H), 7.68 (d, J=2.2, 1/5H), 7.55 (d, J=7.89 Hz, 1H), 7.27 (d, J=8.0 Hz, 1H), 7.06-6.95 (M, 1H), 3.94 (q, J=7.1 Hz, 2H), 3.94 (q, J=7.1 Hz, 2H), 2.37 (d, J=14.9, 1H), 1.90 (d, J=14.9, 1H), 1.60(s, 6H), 1.07 (t, J=7.1 Hz, 3H), FAB-MS calc. for C₂₇H₃₅N₅O₄S : 525 ; Found 526 (M+H)

EXAMPLE C27A



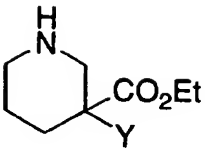
25 Following the same procedures as in Example C27 and using the product d2 from step C, the title compound was prepared. FAB-MS calc. for $C_{27}H_{35}N_5O_4S$: 525 ; Found 526 (M+H)

The additional intermediates shown in Table CX were prepared with the corresponding alkylating agents according to the above established procedure as exemplified in Example C27 steps A and B. The final compounds were prepared according to Example C1 Steps D and E, using Intermediate 1.

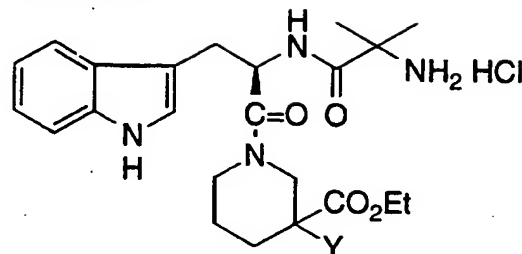
- 341 -

TABLE CX

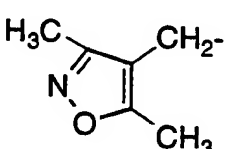
5



Intermediate

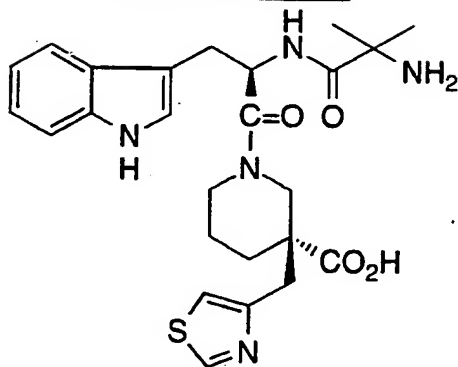


Product

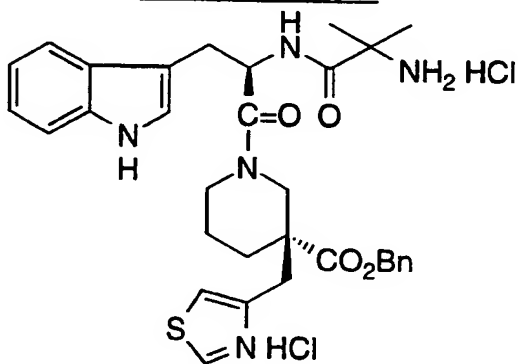
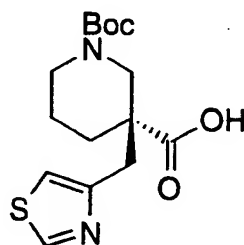
| entry | Y | Intermediate MF | Product MF | isomer |
|-------|---|--|--|--------|
| 1 |  | FAB-MS (M+1) C ₁₄ H ₂₂ N ₂ O ₃ 267 | FAB-MS (M+1) C ₂₉ H ₃₉ N ₅ O ₅ 538 | RS |
| 2 | 2-thiazolylmethyl | C ₁₂ H ₁₈ N ₂ O ₂ S 255 | C ₂₇ H ₃₅ N ₅ O ₄ S 526 | RS |
| 3 | 4-thiazolylmethyl | C ₁₂ H ₁₈ N ₂ O ₂ S 255 | C ₂₇ H ₃₅ N ₅ O ₄ S 526 | RS |
| 4 | 5-thiazolylmethyl | C ₁₂ H ₁₈ N ₂ O ₂ S 255 | C ₂₇ H ₃₅ N ₅ O ₄ S 526 | RS |
| 5 | (4-methyl-2-thiazolyl)methyl | C ₁₃ H ₂₀ N ₂ O ₂ S 269 | C ₂₈ H ₃₇ N ₅ O ₄ S 540 | RS |
| 6 | (2-methyl-4-thiazolyl)methyl | C ₁₃ H ₂₀ N ₂ O ₂ S 269 | C ₂₈ H ₃₇ N ₅ O ₄ S 540 | RS |
| 7 | (4-methyl-5-thiazolyl)methyl | C ₁₃ H ₂₀ N ₂ O ₂ S 269 | C ₂₈ H ₃₇ N ₅ O ₄ S 540 | RS |
| 8 | (5-methyl-4-thiazolyl)methyl | C ₁₃ H ₂₀ N ₂ O ₂ S 269 | C ₂₈ H ₃₇ N ₅ O ₄ S 540 | RS |

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EXAMPLE C28

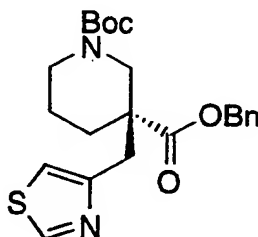
A solution of the final product of Example C27 (50 mg), NaOH (3 N, 5 equiv.) in an mixture of ethanol/water (3:1, 5 mL) was stirred at 60°C for two days. The reaction mixture as then evaporated in vacuo to remove ethanol. The residue was acidified by hydrochloric acid to pH=1 and then evaporated to dryness. The white residue was purified by silica gel column eluting with 3/30/70 NH₄OH/MeOH/CHCl₃ to give the desired product (25 mg). FAB-MS calc. for C₂₅H₃₁N₅O₄S: 497 ; Found 498(M+H)

EXAMPLE C29Step A:

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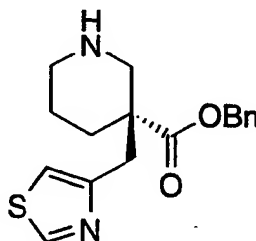
The less polar (d1) intermediate from Example C27 step C (1.5 g, 3.48 mmol) was refluxed for 2 hours in ethanol (10 ml) and 5 N NaOH (3.5 mL). The mixture was then cooled to room temperature and slowly treated with 3 N HCl to pH=11. To this stirred solution was
5 added di-tert-butyl dicarbonate (1.52 g, 7 mmol) and stirred for two hours. The solution was acidified to pH 4 and then neutralized to pH 7 and extracted with ethyl acetate three times. The organic extracts were combined, dried, and concentrated to give white solid (810 mg).

10 Step B:



To a solution of the intermediate from the last step (800 mg), benzyl alcohol (1.27 mL), and DMAP (30 mg) in dichloromethane (40 mL), was added EDC (935 mg, 4.9 mmol). The mixture was stirred at
20 room temperature for three days, and was poured into dilute NaHCO₃ solution. It was extracted with ethyl acetate three times, and dried over MgSO₄. Evaporation and purification by a flash column eluting with 20-40% ethyl acetate in hexane gave the desired product.(145 mg).

25 Step C:

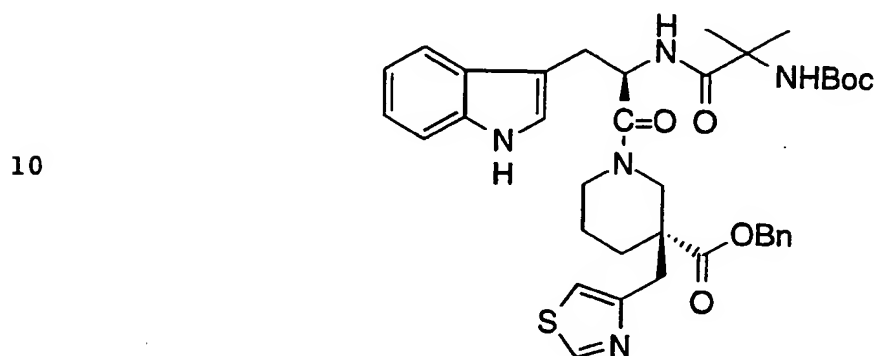


Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (140 mg) in ethyl acetate (20 mL) and HCl gas at 0°C for 15 minutes. After evaporation, the

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residue was dissolved in dichloromethane and the solution was washed with NH_4OH . The organic layer was dried evaporated to give the product.

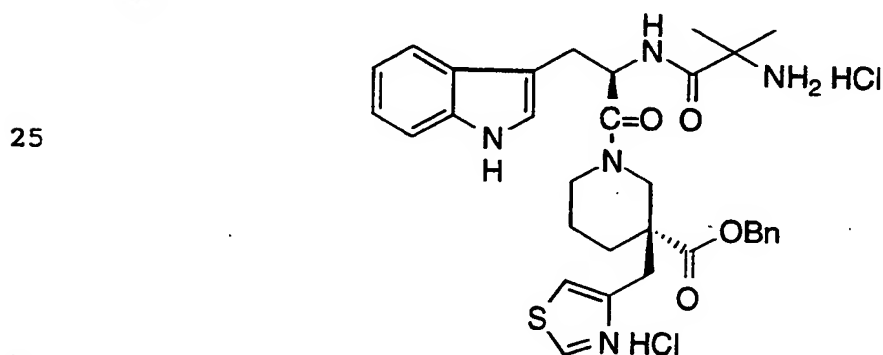
5 Step D:



Prepared by the procedure described in Example C1, Step D from the intermediate prepared in the previous step (140 mg, 0.443 mmol), Intermediate 1 (172 mg, 0.443 mmol), HOBT (60 mg.) and EDC (170 mg). Purification by MPLC, eluting with 80% ethyl acetate in hexane, provided the intermediate (210 mg).

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Step E:

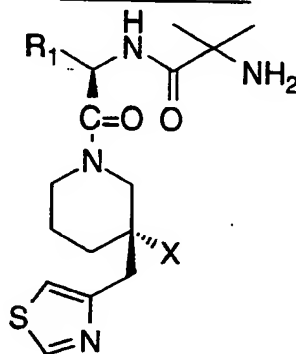


Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (12 mg, 0.018 mmol) and HCl gas in ethyl acetate (3 mL) at 0°C for 10 minutes.

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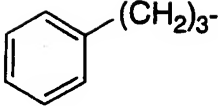
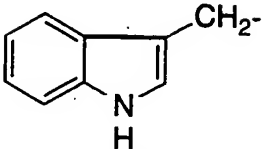
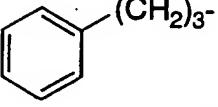
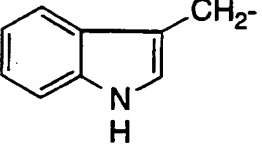
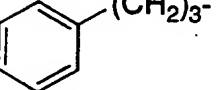
Likewise it is possible to prepare the compounds shown in Table CXa according to this example by reacting the intermediate from Example C29, Step A, with methylamine, ethylamine, ethanolamine, 3-aminopropanol or 2-(methylthio)ethylamine instead of benzyl alcohol in Step B, and using Intermediate 1 or Intermediate 3 in Step D.

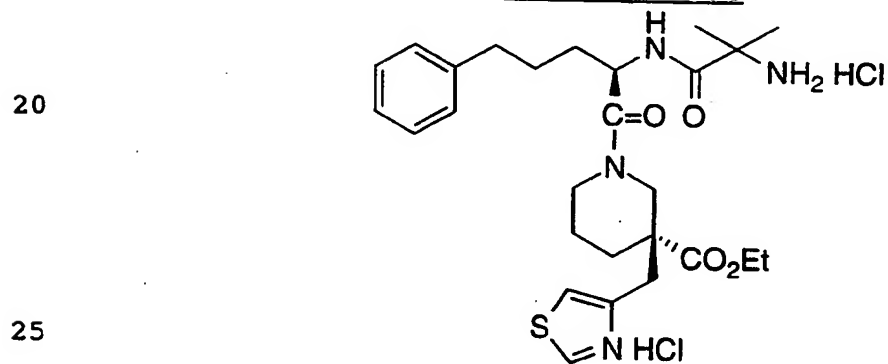
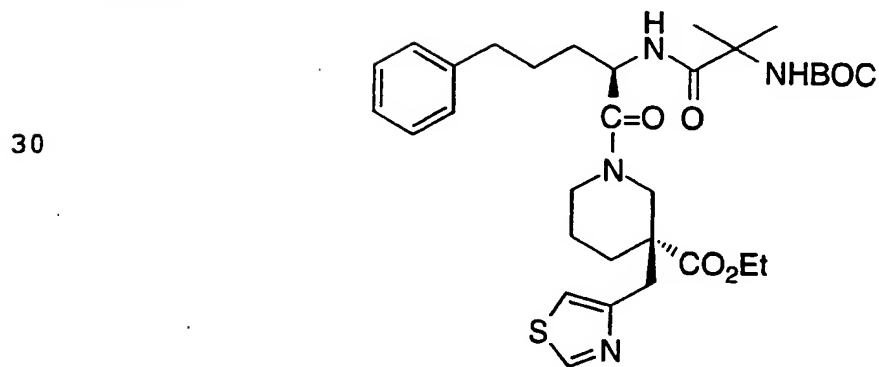
TABLE CXa



| entry | R1 | X |
|-------|----|---|
| 1 | | -CONHCH ₃ |
| 2 | | -CONHCH ₃ |
| 3 | | -CONHCH ₂ CH ₃ |
| 4 | | -CONHCH ₂ CH ₃ |
| 5 | | -CONHCH ₂ CH ₂ OH |

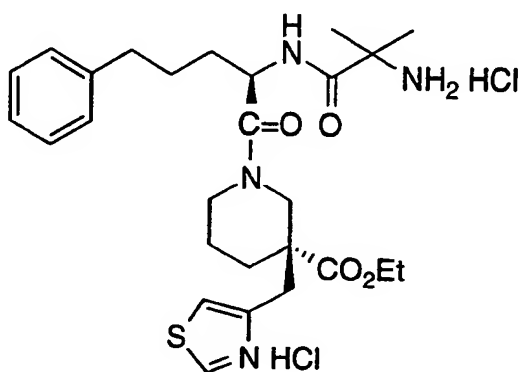
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| | | |
|----|--|---|
| 6 |  | -CONHCH ₂ CH ₂ OH |
| 7 |  | -CONH(CH ₂) ₃ OH |
| 8 |  | -CONH(CH ₂) ₃ OH |
| 9 |  | -CONH(CH ₂) ₂ SCH ₃ |
| 10 |  | -CONH(CH ₂) ₂ SCH ₃ |

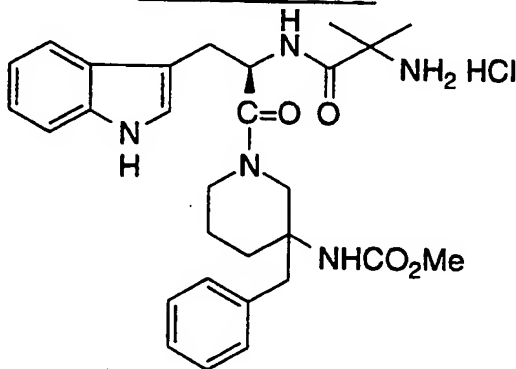
EXAMPLE C30Step A:

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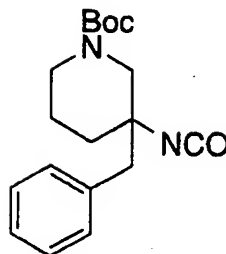
Prepared by the procedure described in Example C1, Step D from the intermediate prepared in Example C27 Step D (134 mg, 0.528 mmol), Intermediate 3 (200 mg, 0.528 mmol), HOBT (71 mg, 1 eq.), and EDC (200 mg, 2 eq.). Purification by MPLC, eluting with 60% ethyl acetate in hexane provided the intermediate (160 mg, 49%)
FAB-MS calc. for C₃₂H₄₆N₄O₆S: 606 ; Found 607 (M+H)

Step B:

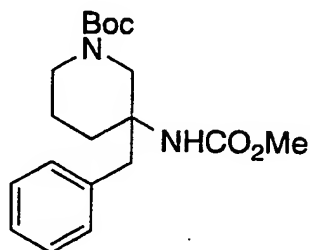
Prepared by the procedure described in Example C1, Step C from the intermediate from the previous step (155 mg, 0.252 mmol) and HCl gas in ethyl acetate (5 mL) at 0°C for 10 minutes (142 mg, 96%).
FAB-MS calc. for C₂₇H₃₈N₄O₄S: 506 ; Found 507 (M+H)

EXAMPLE C31

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Step A:

To a stirred solution of the product from example 15 step A (2.00 g, 6.26 mmol) and DMF (3 drops) in benzene (20 mL) at 0°C, was added oxalyl chloride (0.89 g, 6.89 mmol) slowly. The reaction was stirred at 0°C for 10 minutes and another 20 minutes at room temperature. The reaction mixture was evaporated in vacuo to give the acyl chloride and it was used for the next reaction without further purification. To a stirred solution of the residue in acetone (20 mL) at 5°C, was added sodium azide (1.22 g, 18.8 mmol) in water (3 mL) and the resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was evaporated to remove acetone, and was diluted with water and extracted with ether. The ether extracts were combined and dried over MgSO₄. Filtration and evaporation gave the crude azide and it was used without further purification. The resulting material was dissolved in toluene (70 mL) and was refluxed overnight to give the isocyanate toluene solution. FAB-MS calc. for C₁₈H₂₄N₂O₃: 316; Found 217 (M+H-BOC(100)).

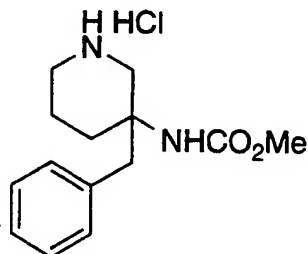
25 Step B:

A solution of methanol (5 mL) and the solution obtained from the last step (15 mL out of 70 mL total, 1.3 mmol) was refluxed

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overnight. The reaction mixture was evaporated to give a white solid (331 mg). FAB-MS calc. for $C_{19}H_{28}N_2O_4$: 348; Found 349 (M+H).

Step C:

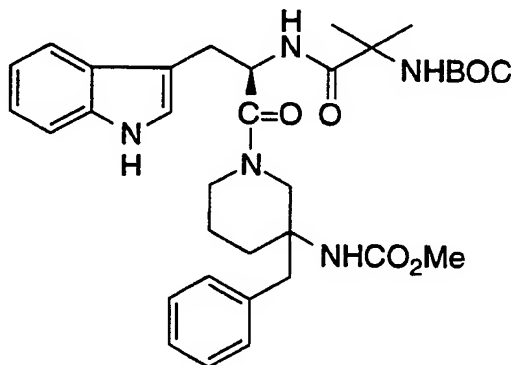


To a solution of the intermediate from the previous step (271 mg) in ethyl acetate (15 mL) at $0^{\circ}C$, was bubbled hydrogen chloride gas until saturation occurred. The reaction was stirred for 30 minutes, until

15

TLC analysis indicated that the reaction was complete. The solution was then concentrated to remove the ethyl acetate to afford the product (284 mg). FAB-MS calc. for $C_{14}H_{20}N_2O_2$: 248; Found 249 (M+H)

Step D:

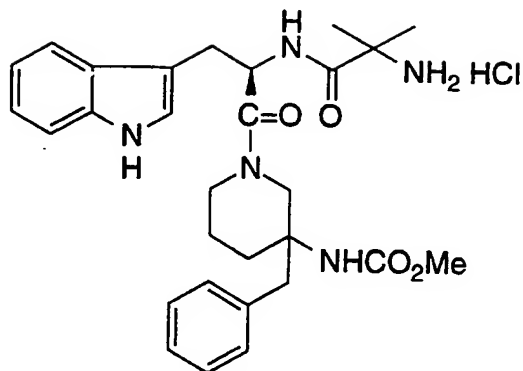


Prepared by the procedure described in Example C1, Step D from the intermediate prepared in the previous step (0.284 g, 1 mmol),

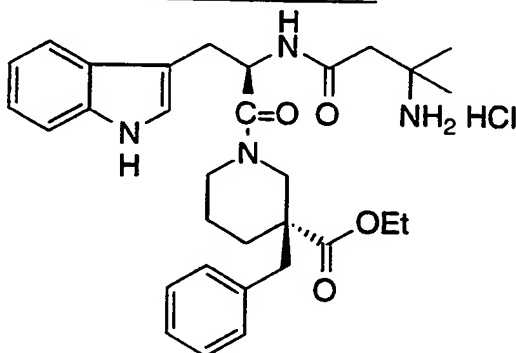
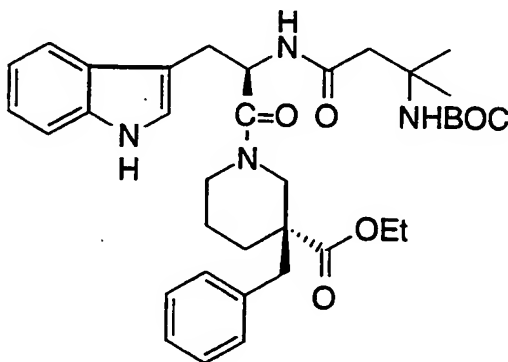
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Intermediate 1 (0.388 g, 1 mmol), HOBT (1 eq.), N-methyl morpholine (1 eq.), and EDC (1.5 eq.). Purification by MPLC, eluting with 60% ethyl acetate in hexane, provided the intermediate (0.35 g). FAB-MS calc. for $C_{34}H_{45}N_5O_6$: 619; Found 620 (M+H)

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Step E:

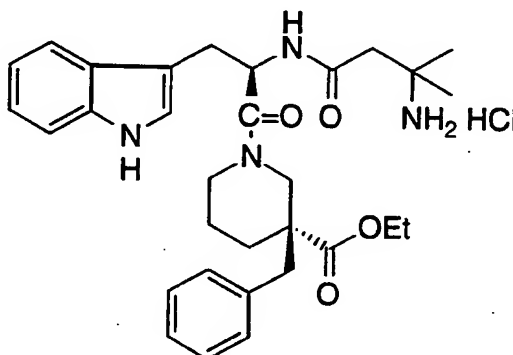
To a solution of the intermediate from the previous step (200 mg, mmol) in ethyl acetate (10 mL) at 0°C, was bubbled hydrogen chloride gas until saturation occurred. The reaction was stirred for 30 minutes, and then concentrated to remove the ethyl acetate to afford the product (158mg). FAB-MS calc. for C₂₉H₃₇N₅O₄: 519; Found 520 (M+H)

EXAMPLE C32Step A:

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To a stirred suspension of the intermediate obtained in Example C2, step C (HCl salt, 2.51 g, 5.34 mmol), N-Boc- β -amino- β -Me-butyric acid (1.16g, 1 equiv.), NMM (0.6 mL, 1 equiv.) and DMAP (33 mg, 0.05 equiv.) in dichloromethane (30 mL), was added EDC (1.55 g, 1.5 equiv.) in several portions. The reaction mixture quickly became clear and it was stirred for 3 hours and was worked up by diluting it with dichloromethane and washing with 3 N HCl, brine, and saturated sodium bicarbonate solution. The organic layer was dried over MgSO₄, evaporated and purified by silica gel column chromatography, eluting with 60% ethyl acetate in hexane to give the desired compound (3.40 g, 100%). FAB-MS calc. for C₃₆H₄₈N₄O₆: 632; Found 633 (M+H)

Step B:

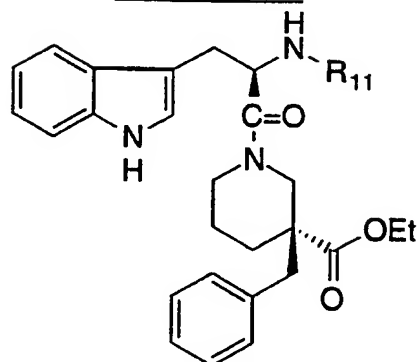


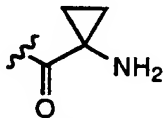
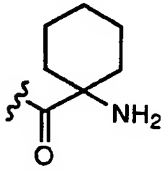
To a stirred solution of the intermediate from the previous step (3.28 g, 5.18 mmol) in ethyl acetate (30 mL) at 0°C, was bubbled HCl gas until it was saturated. The reaction was stirred for 10 minutes, and was evaporated to dryness. The residue was dissolved in dichloromethane, and to which ether was added. The solid which formed was collected by filtration, and it was air dried and left under high vacuum overnight to give the product (2.44g, 83%). FAB-MS calc. for C₃₁H₄₀N₄O₄: 532; Found 533 (M+H)

Similarly the following compounds were prepared according to the same procedure as described above, but using different Boc protected amino acids which were subsequently deprotected as described above.

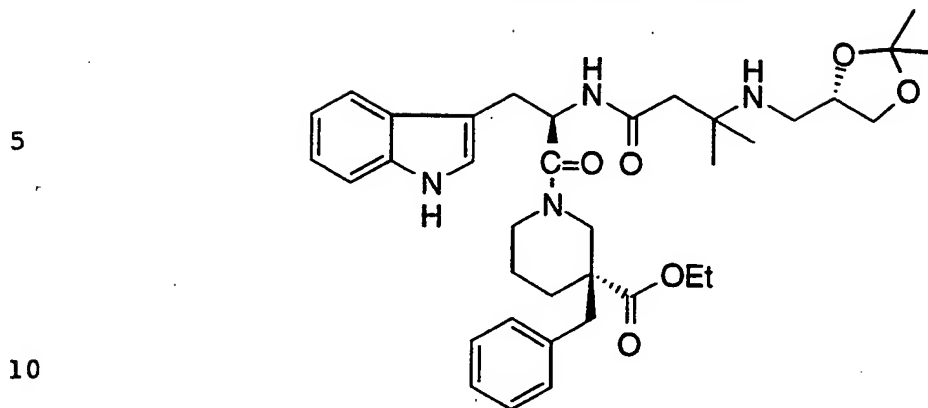
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TABLE CXI



| entry | R11 | MF FAB-MS (M+1) |
|-------|---|--|
| 1 | D-Ala- | C ₂₉ H ₃₆ N ₄ O ₄ 505 |
| 2 | L-Ala- | C ₂₉ H ₃₆ N ₄ O ₄ 505 |
| 3 | β-Ala- | C ₂₉ H ₃₆ N ₄ O ₄ 505 |
| 4 | DL-α-Me-Ser- | C ₃₀ H ₃₈ N ₄ O ₅ 535 |
| 5 |  | C ₃₀ H ₃₆ N ₄ O ₄ 517 |
| 6 |  | C ₃₃ H ₄₂ N ₄ O ₄ 559 |
| 7 | D-Pro- | C ₃₁ H ₃₈ N ₄ O ₄ 531 |
| 8 | N-Me-Aib- | C ₃₁ H ₄₀ N ₄ O ₄ 533 |

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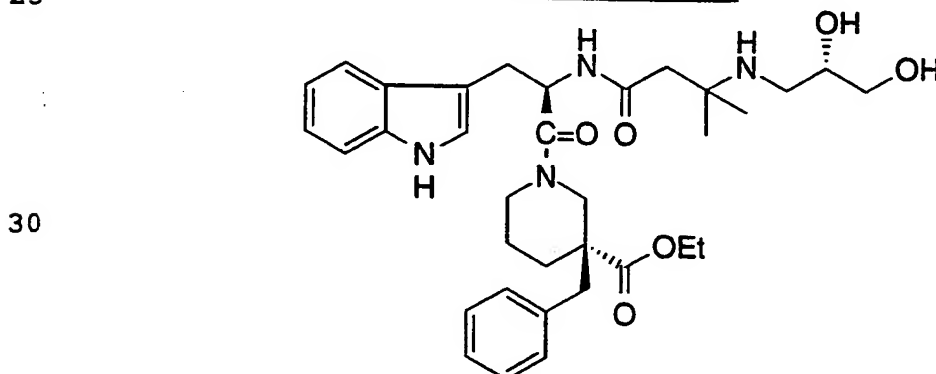
EXAMPLE C33

To a stirred solution of the product from Example C32 (808 mg, 1.42 mmol), (R)-glyceraldehyde acetonide (923 mg, 5 equiv.) and sodium acetate (582 mg, 5 equiv.) in methanol (15 mL) at 0°C, was slowly added sodium cyanoborohydride (134 mg, 1.5 equiv.) and the resulting mixture was stirred at room temperature overnight. The mixture was evaporated to remove methanol and partitioned between sodium bicarbonate solution and dichloromethane. The organic layer was separated and the aqueous layer was extracted two more times with dichloromethane. The combined organic extracts were dried over magnesium sulfate and purified by a silica gel column, eluting with 5-10% methanol in dichloromethane to give the product (835 mg, 91%) FAB-MS calc. for C₃₇H₅₀N₄O₆: 646; Found 647 (M+H)

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EXAMPLE C34

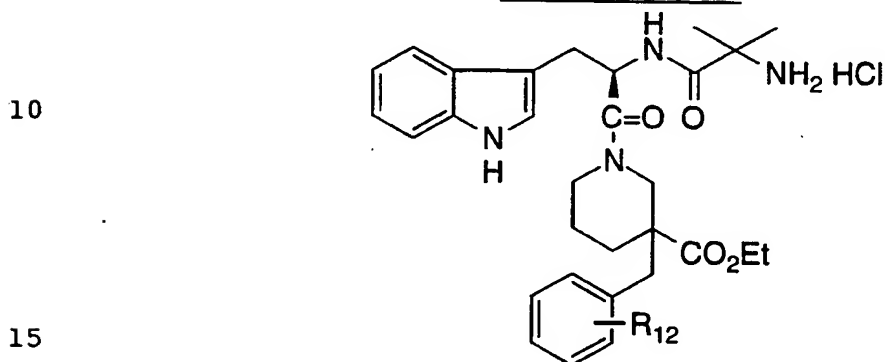
To a solution of the product from Example C33 (367 mg, 0.566 mmol) in methanol (10 mL) was added hydrochloric acid (3 N, 1

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mL) and the resulting mixture was stirred at room temperature for one day. The reaction mixture was evaporated in vacuo, and toluene was added and evaporated in vacuo again to remove the residual water to give the product (350 mg, 99%). FAB-MS calc. for C₃₄H₄₆N₄O₆: 606;

5 Found 607 (M+H)

EXAMPLE C35

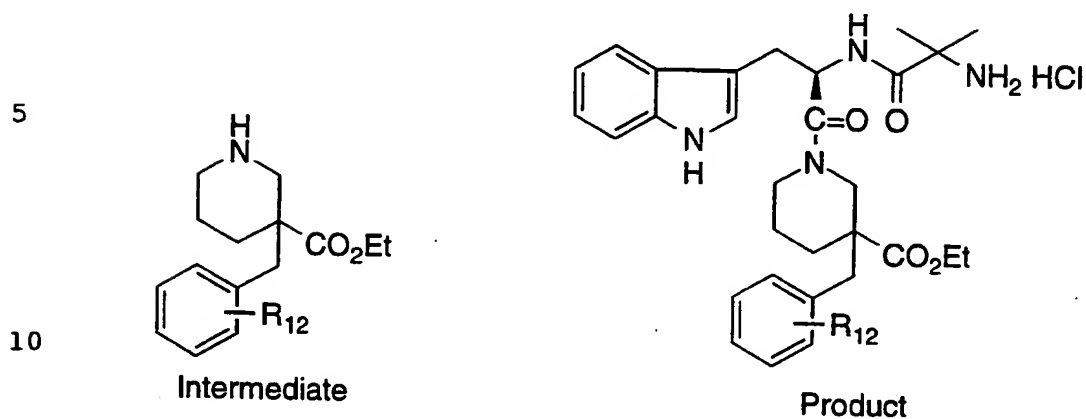


Additional benzyl substituted intermediates and products as shown in Table CXII were prepared according to procedures described in Example C1 Steps A and B using appropriately substituted benzyl halides in the alkylation step. Functional groups changes as needed were made at the intermediate Step B stage to convert as needed cyano groups to carboxamides, esters and tetrazoles, nitro groups to amines and acetylaminos and esters to acids (at step D) according to standard literature procedures.

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TABLE CXII: ADDITIONAL EXAMPLES

| | | Intermediate | Product | | |
|-------|-----------------|-------------------------------|--|--|----------|
| entry | R ₁₂ | MF | MF | isomer | |
| | | FAB-MS (M+1) | FAB-MS (M+1) | | |
| 15 | 1 | <i>o</i> -cyano- | C ₁₆ H ₂₀ N ₂ O ₂ 273 | C ₃₁ H ₃₇ N ₅ O ₄ 544 | d1 d2 |
| | 2 | <i>m</i> -cyano- | C ₁₆ H ₂₀ N ₂ O ₂ 273 | C ₃₁ H ₃₇ N ₅ O ₄ 544 | d1 d2 |
| 20 | 3 | <i>p</i> -cyano- | C ₁₆ H ₂₀ N ₂ O ₂ 273 | C ₃₁ H ₃₇ N ₅ O ₄ 544 | d1 d2 |
| | 4 | <i>p</i> -NH ₂ OC- | C ₁₆ H ₂₂ N ₂ O ₃ 291 | C ₃₁ H ₃₇ N ₅ O ₄ 562 | RS |
| | 5 | <i>p</i> -EtO ₂ C- | C ₁₈ H ₂₅ NO ₄ 320 | C ₃₃ H ₄₂ N ₄ O ₆ 591 | d1 d2 |
| 25 | 6 | <i>p</i> -HO ₂ C- | | C ₃₁ H ₃₈ N ₄ O ₆ 563 | d1 d2 |
| | 7 | <i>p</i> -(1H-tetrazole-5-yl) | C ₁₆ H ₂₁ N ₅ O ₂ 316 | C ₃₁ H ₃₈ N ₈ O ₄ 587 | RS |
| 30 | 8 | <i>m</i> -NH ₂ OC- | C ₁₆ H ₂₂ N ₂ O ₃ 291 | C ₃₁ H ₃₇ N ₅ O ₄ 562 | RS |
| | 9 | <i>m</i> -EtO ₂ C- | C ₁₈ H ₂₅ NO ₄ 320 | C ₃₃ H ₄₂ N ₄ O ₆ 591 | d1 d2 |
| | 10 | <i>m</i> -HO ₂ C- | | C ₃₁ H ₃₈ N ₄ O ₆ 563 | d1 d2 |

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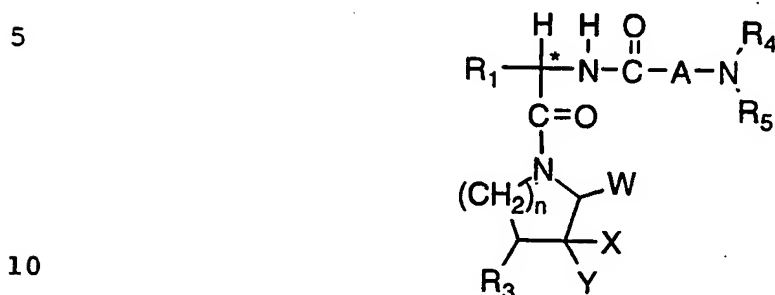
| | | | | |
|-------|-------------------------------|--|--|----------|
| 11 | <i>m</i> -(1H-tetrazole-5-yl) | C ₁₆ H ₂₁ N ₅ O ₂ 316 | C ₃₁ H ₃₈ N ₈ O ₄ 587 | RS |
| 12 | <i>o</i> -NH ₂ OC- | C ₁₆ H ₂₂ N ₂ O ₃ 291 | C ₃₁ H ₃₇ N ₅ O ₄ 562 | RS |
| 5 13 | <i>o</i> -EtO ₂ C- | C ₁₈ H ₂₅ N ₄ O ₄ 320 | C ₃₃ H ₄₂ N ₄ O ₆ 591 | d1 d2 |
| 14 | <i>o</i> -HO ₂ C- | | C ₃₁ H ₃₈ N ₄ O ₆ 563 | d1 d2 |
| 10 15 | <i>o</i> -(1H-tetrazole-5-yl) | C ₁₆ H ₂₁ N ₅ O ₂ 316 | C ₃₁ H ₃₈ N ₈ O ₄ 587 | RS |
| 16 | <i>p</i> -AcNH- | C ₁₇ H ₂₄ N ₂ O ₃ 305 | C ₃₂ H ₄₁ N ₅ O ₅ 576 | RS |
| 15 17 | <i>m</i> -AcNH- | C ₁₇ H ₂₄ N ₂ O ₃ 305 | C ₃₂ H ₄₁ N ₅ O ₅ 576 | RS |

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

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WHAT IS CLAIMED IS:

1. A compound of the formula:



Formula I

wherein:

R₁ is selected from the group consisting of:

- 15 C₁-C₁₀ alkyl, aryl, aryl(C₁-C₆ alkyl), (C₃-C₇ cycloalkyl)(C₁-C₆ alkyl)-, (C₁-C₅ alkyl)-K-(C₁-C₅ alkyl)-, aryl(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, and (C₃-C₇ cycloalkyl)(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, where K is O, S(O)_m, N(R₂)C(O), C(O)N(R₂), OC(O), C(O)O, -CR₂=CR₂-, or -C≡C-, where aryl is selected from: phenyl, naphthyl, indolyl, azaindole,
- 20 pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl, and R₂ and alkyl may be further substituted by 1 to 9 halogen, S(O)_mR_{2a}, 1 to 3 of OR_{2a} or C(O)OR_{2a}, and aryl may be further substituted by 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of OR₂, methylenedioxy, -S(O)_mR₂, 1 to 2 of -CF₃, -OCF₃, nitro, -N(R₂)C(O)(R₂), -C(O)OR₂,
- 25 -C(O)N(R₂)(R₂), -1H-tetrazol-5-yl, -SO₂N(R₂)(R₂), -N(R₂)SO₂ phenyl, or -N(R₂)SO₂R₂;

R₂ is selected from: hydrogen, C₁-C₆ alkyl, and C₃-C₇ cycloalkyl, and where two C₁-C₆ alkyl groups are present on one atom, they may be

30 optionally joined to form a C₃-C₈ cyclic ring, optionally including oxygen, sulfur or NR_{3a};

R_{2a} is hydrogen, or C₁-C₆ alkyl optionally substituted by hydroxyl;

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R₃ is selected from: hydrogen, -(CH₂)_rphenyl, -(CH₂)_rnaphthyl, -C₁-C₁₀ alkyl, -C₃-C₇ cycloalkyl, where the phenyl, naphthyl and C₃-C₇ cycloalkyl rings may be substituted by 1 to 3 substituents selected from the group consisting of:

5 -(CH₂)_rOR₆, -(CH₂)_rN(R₂)(R₆), -(CH₂)_r(R₆), -(CH₂)_rC(O)OR₂,
 -(CH₂)_rC(O)OR₆, -(CH₂)_rOC(O)R₂, -(CH₂)_rOC(O)R₆,
 -(CH₂)_rC(O)R₂, -(CH₂)_rC(O)R₆, -(CH₂)_rC(O)N(R₂)(R₂),
 -(CH₂)_rC(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)R₂, -(CH₂)_rN(R₂)C(O)R₆,
 -(CH₂)_rN(R₆)C(O)R₂, -(CH₂)_rN(R₆)C(O)R₆, -(CH₂)_rN(R₂)C(O)OR₂,
 10 -(CH₂)_rN(R₂)C(O)OR₆, -(CH₂)_rN(R₆)C(O)OR₂,
 -(CH₂)_rN(R₆)C(O)OR₆, -(CH₂)_rN(R₂)C(O)N(R₂)(R₆),
 -(CH₂)_rN(R₂)C(O)N(R₂)(R₂), -(CH₂)_rN(R₆)C(O)N(R₂)(R₆),
 (CH₂)_rN(R₂)SO₂R₆, -(CH₂)_rN(R₂)SO₂R₂, -(CH₂)_rN(R₆)SO₂R₂,
 (CH₂)_rN(R₆)SO₂R₆, -(CH₂)_rOC(O)N(R₂)(R₆),
 15 -(CH₂)_rOC(O)N(R₂)(R₂), -(CH₂)_rSO₂N(R₂)(R₆),
 -(CH₂)_rSO₂N(R₂)(R₂), (CH₂)_rSO₂NHC(O)R₆, -(CH₂)_rSO₂NHC(O)R₂,
 -(CH₂)_rSO₂NHC(O)OR₆, -(CH₂)_rSO₂NHC(O)OR₂,
 -(CH₂)_rC(O)NHC(O)NR₂, -(CH₂)_rC(O)NHC(O)NR₆,
 -(CH₂)_rC(O)NHC(O)R₂, -(CH₂)_rCONHC(O)R₆,
 20 -(CH₂)_rCONHSO₂R₆, -(CH₂)_rCONHSO₂R₂,
 -(CH₂)_rCONHSO₂N(R₂)R₂, -(CH₂)_rCONHSO₂N(R₂)R₆,
 -(CH₂)_rN(R₂)SO₂N(R₂)R₆, -(CH₂)_rN(R₆)SO₂N(R₂)R₆,
 -(CH₂)_rS(O)_mR₆, and -(CH₂)_rS(O)_mR₂;

25 R_{3a} is hydrogen, or C₁-C₆ alkyl optionally substituted by hydroxyl;

W is selected from the group consisting of: hydrogen,
 -CN, -C(O)OR₈, -C(O)OR₂, -C(O)O(CH₂)_laryl, -C(O)N(R₂)(R₂);
 -C(O)N(R₂)(R₈), -C(O)N(R₂)(CH₂)_laryl, -CH₂N(R₂)C(O)R₈
 30 -CH₂N(R₂)C(O)(CH₂)_laryl, -(CH₂)_rOR₂, -CH(OH)R₂,
 -CH(OH)(CH₂)_laryl, -C(O)R₂, -C(O)(CH₂)_laryl, 1H-tetrazol-5-yl,
 5-amino-1, 2, 4-oxadiazol-3-yl, and 5-methyl-1, 2, 4-oxadiazol-3-yl,
 where R₈ is hydrogen, C₁-C₆ alkyl, or C₁-C₆ alkyl substituted by
 OR₂, C(O)OR₂, CON(R₂)(R₂), N(R₂)C(O)R₂,

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$N(R_2)C(O)N(R_2)(R_2)$, and aryl is phenyl, pyridyl, or 1H-tetrazol-5-yl;

X is selected from the group consisting of: hydrogen, $-C\equiv N$,
 5 $-(CH_2)_qN(R_2)C(O)R_2$, $-(CH_2)_qN(R_2)C(O)(CH_2)_t\text{aryl}$,
 $-(CH_2)_qN(R_2)SO_2(CH_2)_t\text{aryl}$, $-(CH_2)_qN(R_2)SO_2R_2$,
 $-(CH_2)_qN(R_2)C(O)N(R_2)(CH_2)_t\text{aryl}$, $-(CH_2)_qN(R_2)C(O)N(R_2)(R_2)$,
 $-(CH_2)_qC(O)N(R_2)(R_2)$, $-(CH_2)_qC(O)N(R_2)(CH_2)_t\text{aryl}$,
 $-(CH_2)_qC(O)OR_2$, $-(CH_2)_qC(O)O(CH_2)_t\text{aryl}$, $-(CH_2)_qOR_2$,
 10 $-(CH_2)_qOC(O)R_2$, $-(CH_2)_qOC(O)(CH_2)_t\text{aryl}$,
 $-(CH_2)_qOC(O)N(R_2)(CH_2)_t\text{aryl}$, $-(CH_2)_qOC(O)N(R_2)(R_2)$,
 $-(CH_2)_qC(O)R_2$, $-(CH_2)_qC(O)(CH_2)_t\text{aryl}$,
 $-(CH_2)_qN(R_2)C(O)OR_2$, $-(CH_2)_qN(R_2)SO_2N(R_2)(R_2)$,
 $-(CH_2)_qS(O)_mR_2$, and $-(CH_2)_qS(O)_m(CH_2)_t\text{aryl}$, where an R_2 , $(CH_2)_q$
 15 and $(CH_2)_t$ group may be optionally substituted by 1 to 2 C₁-C₄ alkyl,
 hydroxyl, C₁-C₄ lower alkoxy, carboxyl, CONH₂, S(O)_mCH₃,
 carboxylate C₁-C₄ alkyl esters, or 1H-tetrazol-5-yl, and aryl is phenyl,
 naphthyl, pyridyl, thiazolyl, or 1H-tetrazol-5-yl groups which may be
 optionally substituted by 1 to 3 halogen, 1 to 3 -OR₂, -CON(R₂)(R₂),
 20 $-C(O)OR_2$, 1 to 3 C₁-C₄ alkyl, -S(O)_mR₂, or 1H-tetrazol-5-yl;

Y is selected from the group consisting of:
 hydrogen, C₁-C₁₀ alkyl, $-(CH_2)_t\text{aryl}$,
 $-(CH_2)_q(C_3-C_7 \text{ cycloalkyl})$, $-(CH_2)_q-K-(C_1-C_6 \text{ alkyl})$,
 25 $-(CH_2)_q-K-(CH_2)_t\text{aryl}$, $-(CH_2)_q-K-(CH_2)_t(C_3-C_7 \text{ cycloalkyl})$
 containing O, NR₂, S), and $-(CH_2)_q-K-(CH_2)_t(C_3-C_7 \text{ cycloalkyl})$, where
 K is O, S(O)_m, C(O)NR₂, CH=CH, C≡C, N(R₂)C(O), C(O)NR₂, C(O)O,
 or OC(O), and where the alkyl, R₂, $(CH_2)_q$ and $(CH_2)_t$ groups may be
 optionally substituted by C₁-C₄ alkyl, hydroxyl, C₁-C₄ lower alkoxy,
 30 carboxyl, -CONH₂ or carboxylate C₁-C₄ alkyl esters, and aryl is phenyl,
 naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl,
 pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiophenyl,
 quinolinyl, pyrraziny, or isothiazolyl which is optionally substituted by 1

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to 3 halogen, 1 to 3 -OR₂, -C(O)OR₂, -C(O)N(R₂)(R₂), nitro, cyano, benzyl, 1 to 3 C₁-C₄ alkyl, -S(O)_mR₂, or 1H-tetrazol-5-yl; with the proviso that at least one of R₃, W, X, and Y are other than hydrogen;

5

R₄ and R₅ are independently hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C₁-C₁₀ alkanoyloxy, 1 to 3 C₁-C₆ alkoxy, phenyl, phenoxy, 2-furyl, C₁-C₆ alkoxy carbonyl, S(O)_m(C₁-C₆ alkyl); or R₄ and R₅ can be taken together to form -(CH₂)_dL_a(CH₂)_e- where L_a is C(R₂)₂, O, S(O)_m or N(R₂), d and e are independently 1 to 3 and R₂ is as defined above;

10

A is:

15



20

where x and y are independently 0, 1, 2 or 3;

Z is N-R_{6a} or O, where R_{6a} is hydrogen or C₁-C₆ alkyl;

25

R₆ is hydrogen, C₁-C₆ alkyl, or (CH₂)_varyl, wherein the alkyl and (CH₂)_v groups may be optionally substituted by 1-2 O(R₂), S(O)_mR₂, 1H-tetrazol-5-yl, C(O)OR₂, C(O)N(R₂)(R₂) or SO₂N(R₂)(R₂), N(R₂)C(O)N(R₂)(R₂), and wherein aryl is phenyl, pyridyl, 1H-tetrazol-5-yl, triazolyl, imidazolyl, thiazolyl, pyrazolyl, thiadiazolyl, imidazolone-1-yl, benzimidazol-2-yl, triazolinone-yl optionally substituted with C₁-C₆ alkyl, C₃-C₆ cycloalkyl, amino, or hydroxyl;

30

R₇ and R_{7a} are independently hydrogen, C₁-C₆ alkyl, trifluoromethyl, phenyl, substituted C₁-C₆ alkyl where the substituents are imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)_mR₂, C(O)O(C₁-C₆ alkyl),

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C3-C7 cycloalkyl, N(R2)(R2), C(O)N(R2)(R2); or R7 and R7a can independently be joined to one or both of R4 and R5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R7 or R7a groups, wherein the bridge contains 1 to 5 carbons atoms; or R7 and R7a can be joined to one another to form a C3-C7 cycloalkyl;

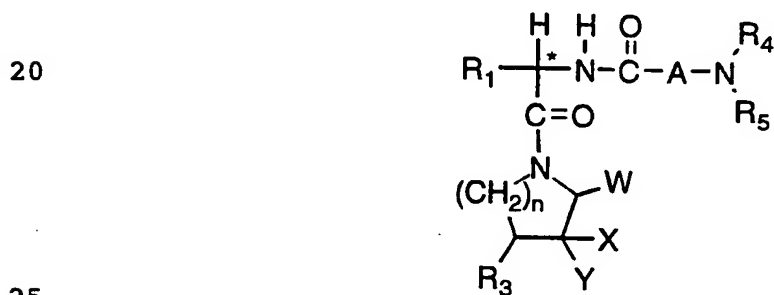
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1 is 0, 1 or 2;
m is 0, 1, or 2;
n is 1, 2, or 3;
10 q is 0, 1, 2, 3, or 4;
r is 0, 1, 2, or 3;
t is 0, 1, 2, or 3;
v is 0, 1, or 2 ;

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15 and pharmaceutically acceptable salts and individual diastereomers thereof.

2. A compound of the formula:



Formula AI

wherein:

R₁ is selected from the group consisting of:

30 C₁-C₁₀ alkyl, aryl, aryl(C₁-C₆ alkyl), (C₃-C₇ cycloalkyl)(C₁-C₆ alkyl)-, (C₁-C₅ alkyl)-K-(C₁-C₅ alkyl)-, aryl(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, and (C₃-C₇ cycloalkyl)(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, where K is O, S(O)_m, N(R₂)C(O), C(O)N(R₂), OC(O), C(O)O, -CR₂=CR₂-, or -C≡C-, where aryl is selected from: phenyl, naphthyl, indolyl, azaindole, pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl, and R₂ and alkyl may be further substituted by 1 to 9 halogen, S(O)_mR_{2a}, 1

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to 3 of OR_{2a} or C(O)OR_{2a}, and aryl may be further substituted by 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of OR₂, methylenedioxy, -S(O)_mR₂, 1 to 2 of -CF₃, -OCF₃, nitro, -N(R₂)C(O)(R₂), -C(O)OR₂, -C(O)N(R₂)(R₂), -1H-tetrazol-5-yl, -SO₂N(R₂)(R₂), -N(R₂)SO₂ phenyl, or -N(R₂)SO₂R₂;

R₂ is selected from: hydrogen, C₁-C₆ alkyl, and C₃-C₇ cycloalkyl, and where two C₁-C₆ alkyl groups are present on one atom, they may be optionally joined to form a C₃-C₈ cyclic ring, optionally including oxygen, sulfur or NR_{3a};

R_{2a} is hydrogen, or C₁-C₆ alkyl optionally substituted by hydroxyl;

R₃ is selected from: hydrogen, -(CH₂)_rphenyl, -(CH₂)_rnaphthyl, -C₁-C₁₀ alkyl, -C₃-C₇ cycloalkyl, where the phenyl, naphthyl and C₃-C₇ cycloalkyl rings may be substituted by 1 to 3 substituents selected from the group consisting of: C₁-C₆ alkyl, halogen, -OR₂, -NHSO₂CF₃, -(CH₂)_rOR₆, -(CH₂)_rN(R₂)(R₆), -(CH₂)_r(R₆), -(CH₂)_rC(O)OR₂, -(CH₂)_rC(O)OR₆, -(CH₂)_rOC(O)R₂, -(CH₂)_rOC(O)R₆, -(CH₂)_rC(O)R₂, -(CH₂)_rC(O)R₆, -(CH₂)_rC(O)N(R₂)(R₂), -(CH₂)_rC(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)R₂, -(CH₂)_rN(R₂)C(O)R₆, -(CH₂)_rN(R₆)C(O)R₂, -(CH₂)_rN(R₆)C(O)R₆, -(CH₂)_rN(R₂)C(O)OR₂, -(CH₂)_rN(R₂)C(O)OR₆, -(CH₂)_rN(R₆)C(O)OR₂, -(CH₂)_rN(R₆)C(O)OR₆, -(CH₂)_rN(R₂)C(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)N(R₂)(R₂), -(CH₂)_rN(R₆)C(O)N(R₂)(R₆), -(CH₂)_rN(R₂)SO₂R₆, -(CH₂)_rN(R₂)SO₂R₂, -(CH₂)_rN(R₆)SO₂R₂, -(CH₂)_rN(R₆)SO₂R₆, -(CH₂)_rOC(O)N(R₂)(R₆), -(CH₂)_rOC(O)N(R₂)(R₂), -(CH₂)_rSO₂N(R₂)(R₆), -(CH₂)_rSO₂N(R₂)(R₂), -(CH₂)_rSO₂NHC(O)R₆, -(CH₂)_rSO₂NHC(O)R₂, -(CH₂)_rSO₂NHC(O)OR₆, -(CH₂)_rSO₂NHC(O)OR₂, -(CH₂)_rC(O)NHC(O)NR₂, -(CH₂)_rC(O)NHC(O)NR₆, -(CH₂)_rC(O)NHC(O)R₂, -(CH₂)_rCONHC(O)R₆, -(CH₂)_rCONHSO₂R₆, -(CH₂)_rCONHSO₂R₂, -(CH₂)_rCONHSO₂N(R₂)(R₂), -(CH₂)_rCONHSO₂N(R₂)(R₆),

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$-(CH_2)_rN(R_2)SO_2N(R_2)R_6$, $-(CH_2)_rN(R_6)SO_2N(R_2)(R_6)$,
 $-(CH_2)_rS(O)_mR_6$, and $-(CH_2)_rS(O)_mR_2$;

5 R_{3a} is hydrogen, or C₁-C₆ alkyl optionally substituted by hydroxyl;

W is selected from the group consisting of:

-CN, -C(O)OR₈, -C(O)OR₂, -C(O)O(CH₂)_laryl, -C(O)N(R₂)(R₂);
 -C(O)N(R₂)(R₈), -C(O)N(R₂)(CH₂)_laryl, -CH₂N(R₂)C(O)R₈
 -CH₂N(R₂)C(O)(CH₂)_laryl, -(CH₂)_rOR₂, -CH(OH)R₂,
 10 -CH(OH)(CH₂)_laryl, -C(O)R₂, -C(O)(CH₂)_laryl, 1H-tetrazol-5-yl,
 5-amino-1, 2, 4-oxadiazol-3-yl, and 5-methyl-1, 2, 4-oxadiazol-3-yl,
 where R₈ is hydrogen, C₁-C₆ alkyl, or C₁-C₆ alkyl substituted by
 OR₂, C(O)OR₂, CON(R₂)(R₂), N(R₂)C(O)R₂,
 15 N(R₂)C(O)N(R₂)(R₂), and aryl is phenyl, pyridyl, or 1H-tetrazol-5-yl;

X is selected from: hydrogen, -C≡N, -(CH₂)_qN(R₂)C(O)R₂,
 -(CH₂)_qN(R₂)C(O)(CH₂)_taryl, -(CH₂)_qN(R₂)SO₂(CH₂)_taryl,
 -(CH₂)_qN(R₂)SO₂R₂, -(CH₂)_qN(R₂)C(O)N(R₂)(CH₂)_taryl,
 20 -(CH₂)_qN(R₂)C(O)N(R₂)(R₂), -(CH₂)_qC(O)N(R₂)(R₂),
 -(CH₂)_qC(O)N(R₂)(CH₂)_taryl, -(CH₂)_qC(O)OR₂,
 -(CH₂)_qC(O)O(CH₂)_taryl, -(CH₂)_qOR₂, -(CH₂)_qOC(O)R₂,
 -(CH₂)_qOC(O)(CH₂)_taryl, -(CH₂)_qOC(O)N(R₂)(CH₂)_taryl,
 -(CH₂)_qOC(O)N(R₂)(R₂), -(CH₂)_qC(O)R₂, -(CH₂)_qC(O)(CH₂)_taryl,
 25 -(CH₂)_qN(R₂)C(O)OR₂, -(CH₂)_qN(R₂)SO₂N(R₂)(R₂),
 -(CH₂)_qS(O)_mR₂, and -(CH₂)_qS(O)_m(CH₂)_taryl, where an R₂, (CH₂)_q
 and (CH₂)_t group may be optionally substituted by 1 to 2 C₁-C₄ alkyl,
 hydroxyl, C₁-C₄ lower alkoxy, carboxyl, CONH₂, S(O)_mCH₃,
 carboxylate C₁-C₄ alkyl esters, or 1H-tetrazol-5-yl, and aryl is phenyl,
 30 naphthyl, pyridyl, thiazolyl, or 1H-tetrazol-5-yl groups which may be
 optionally substituted by 1 to 3 halogen, 1 to 3 -OR₂, -CON(R₂)(R₂),
 -C(O)OR₂, 1 to 3 C₁-C₄ alkyl, -S(O)_mR₂, or 1H-tetrazol-5-yl;

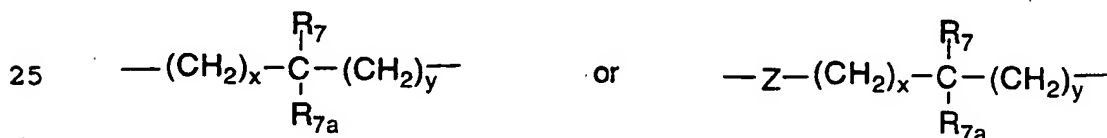
Y is selected from: hydrogen, C₁-C₁₀ alkyl, -(CH₂)_taryl,

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-(CH₂)_q(C₃-C₇ cycloalkyl), -(CH₂)_q-K-(C₁-C₆ alkyl),
 -(CH₂)_q-K-(CH₂)_taryl, -(CH₂)_q-K-(CH₂)_t(C₃-C₇ cycloalkyl)
 containing O, NR₂, S), and -(CH₂)_q-K-(CH₂)_t(C₃-C₇ cycloalkyl), where
 K is O, S(O)_m, C(O)NR₂, CH=CH, C≡C, N(R₂)C(O), C(O)NR₂, C(O)O,
 5 or OC(O), and where the alkyl, R₂, (CH₂)_q and (CH₂)_t groups may be
 optionally substituted by C₁-C₄ alkyl, hydroxyl, C₁-C₄ lower alkoxy,
 carboxyl, -CONH₂ or carboxylate C₁-C₄ alkyl esters, and aryl is phenyl,
 naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl,
 pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiophenyl,
 10 quinoliny, pyrraziny, or isothiazolyl which is optionally substituted by 1
 to 3 halogen, 1 to 3 -OR₂, -C(O)OR₂, -C(O)N(R₂)(R₂), nitro, cyano,
 benzyl, 1 to 3 C₁-C₄ alkyl, -S(O)_mR₂, or 1H-tetrazol-5-yl;

15 R₄ and R₅ are independently hydrogen, C₁-C₆ alkyl, substituted C₁-
 C₆ alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxy, 1
 to 3 C₁-C₁₀ alkanoyloxy, 1 to 3 C₁-C₆ alkoxy, phenyl, phenoxy, 2-
 furyl, C₁-C₆ alkoxy carbonyl, S(O)_m(C₁-C₆ alkyl); or R₄ and R₅ can
 be taken together to form -(CH₂)_dL_a(CH₂)_e- where L_a is C(R₂)₂, O,
 20 S(O)_m or N(R₂), d and e are independently 1 to 3 and R₂ is as defined
 above;

A is:



where x and y are independently 0, 1, 2 or 3;

30 Z is N-R_{6a} or O, where R_{6a} is hydrogen or C₁-C₆ alkyl;

R₆ is hydrogen, C₁-C₆ alkyl, or (CH₂)_varyl, wherein the alkyl and
 (CH₂)_v groups may be optionally substituted by 1-2 O(R₂), S(O)_mR₂,
 1H-tetrazol-5-yl, C(O)OR₂, C(O)N(R₂)(R₂) or SO₂N(R₂)(R₂),
 N(R₂)C(O)N(R₂)(R₂), and wherein aryl is phenyl, pyridyl, 1H-tetrazol-

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5-yl, triazolyl, imidazolyl, thiazolyl, pyrazolyl, thiadiazolyl, imidazolone-1-yl, benzimidazol-2-yl, triazolinone-yl optionally substituted with C₁-C₆ alkyl, C₃-C₆ cycloalkyl, amino, or hydroxyl;

- 5 R₇ and R_{7a} are independently hydrogen, C₁-C₆ alkyl, trifluoromethyl, phenyl, substituted C₁-C₆ alkyl where the substituents are imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)_mR₂, C(O)O(C₁-C₆ alkyl), C₃-C₇ cycloalkyl, N(R₂)(R₂), C(O)N(R₂)(R₂); or R₇ and R_{7a} can
10 independently be joined to one or both of R₄ and R₅ groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R₇ or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms; or R₇ and R_{7a} can be joined to one another to form a C₃-C₇ cycloalkyl;

- l is 0, 1 or 2;
15 m is 0, 1, or 2;
n is 1, 2, or 3;
q is 0, 1, 2, 3, or 4;
r is 0, 1, 2, or 3;
t is 0, 1, 2, or 3;
v is 0, 1, or 2 ;
20 and pharmaceutically acceptable salts and individual diastereomers thereof.

25

30

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3. The compound of Claim 2 wherein:

R₁ is selected from the group consisting of:

5 C₁-C₁₀ alkyl, aryl (C₁-C₄ alkyl)-, C₃-C₆ cycloalkyl (C₁-C₄ alkyl)-, (C₁-C₄ alkyl)-K-(C₁-C₂ alkyl)-, aryl (C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-, and (C₃-C₇ cycloalkyl)(C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-, where K is O, S(O)_m, OC(O), C(O)O and the alkyl groups may be further substituted by 1 to 7 halogen, S(O)_mR₂, 1 to 3 OR₂ or C(O)OR₂ and aryl is phenyl, naphthyl, indolyl, pyridyl, benzothienyl, or benzofuranyl which may be
10 further substituted by 1-2 C₁-C₄ alkyl, 1 to 2 halogen, 1 to 2 OR₂, S(O)_mR₂ or C(O)OR₂;

R₂ is hydrogen, C₁-C₆ alkyl, or C₃-C₇ cycloalkyl and where two C₁-C₆ alkyl groups are present on one atom they may be optionally joined to
15 form a C₄-C₇ cyclic ring optionally including oxygen, sulfur or NR_{3a};

R₃ is hydrogen or phenyl optionally substituted in the ortho position by a C₁-C₆ alkyl group, -NHSO₂CF₃, -(CH₂)_r (1H-tetrazol-5-yl), -(CH₂)_rC(O)OR₂, (CH₂)_rC(O)N(R₂)(R₆);
20

R_{3a} is hydrogen, or C₁-C₄ alkyl;

W is -CN, -C(O)OR₂, -C(O)N(R₂)(R₂), -C(O)N(R₂)(CH₂)₁ phenyl, 1H-tetrazol-5-yl, or -(CH₂)_rOR₂;
25

X is hydrogen, -(CH₂)_qC(O)N(R₂)(R₆), or -(CH₂)_qC(O)OR₂;

Y is hydrogen, C₁-C₈ alkyl, -(CH₂)_t phenyl, -(CH₂)_t pyridyl, or -(CH₂)_tthiazolyl;
30

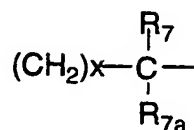
R₄ and R₅ are independently hydrogen, C₁-C₆ alkyl, or substituted C₁-C₆ alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxyl, S(O)_m (C₁-C₆ alkyl) or phenyl;

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R₆ is hydrogen, or C₁-C₆ alkyl;

A is:

5



where x is 0, or 1;

10

R₇ and R_{7a} are independently hydrogen C₁-C₆ alkyl, trifluoromethyl, phenyl, substituted C₁-C₆ alkyl where the substituents are imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)_mR₂, C(O)O(C₁-C₆ alkyl), C₅-C₇ cycloalkyl, N(R₂)(R₂), C(O)N(R₂)(R₂); or R₇ and R_{7a} can

15

independently be joined to one of R₄ or R₅ to form alkylene bridges between the terminal nitrogen and the alkyl portion of R₇ or R_{7a} groups to form 5 or 6 membered rings; or R₇ and R_{7a} can be joined to one another to form a C₃ cycloalkyl;

20

l is 0 or 1;

n is 2;

m is 0, 1, or 2;

r is 0, 1, 2 or 3;

q is 0 or 1

25

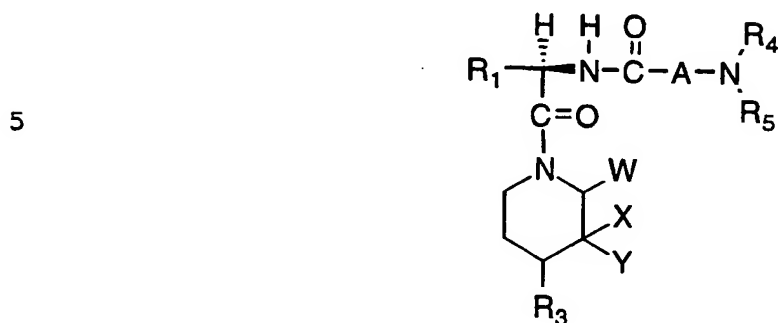
t is 0 or 1;

and pharmaceutically acceptable salts and individual diastereomers thereof.

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4. The compound of Claim 2 of the formula:



Formula AIb

wherein:

R1 is selected from the group consisting of: C1-C10 alkyl, aryl (C1-C3 alkyl)-, and aryl (C0-C1 alkyl)-K-(C1-C2 alkyl)-, where K is
 15 O or S(O)m and the aryl is phenyl, pyridyl, naphthyl, or indolyl which are optionally substituted by 1-2 C1-C4 alkyl, 1 to 2 halogen, 1 to 2 OR2, S(O)m R2 or C(O)OR2;

R2 is hydrogen, C1-C6 alkyl, or C3-C7 cycloalkyl and where two C1-C6
 20 alkyl groups are present on one atom they may be optionally joined to form a C5-C7 cyclic ring optionally including oxygen, sulfur or NR3a;

R3 is hydrogen or phenyl optionally substituted in the ortho position by a C1-C3 alkyl group, (CH2)r(1H-tetrazol-5-yl) or (CH2)rC(O)OR2;

25 R3a is hydrogen, or C1-C4 alkyl;

W is -CN, -C(O)OR2, or -C(O)N(R2)R2);

30 X is hydrogen or C(O)OR2;

Y is hydrogen, benzyl, picoyl, or thiazolylmethyl;

R4 and R5 are independently hydrogen, C1-C3 alkyl, substituted C1-C3 alkyl where the substituents may be 1 to 2 hydroxyl;

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A is:



where x is 0, or 1;

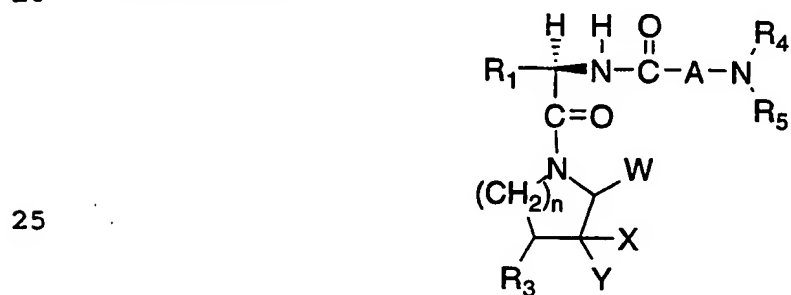
10 R₇ and R_{7a} are independently hydrogen or C₁-C₄ alkyl;

m is 0, 1, or 2;

r is 0, 1, or 2;

15 and pharmaceutically acceptable salts and individual diastereomers thereof.

20 5. The stereospecifically defined compound of Claim 2 of the formula:

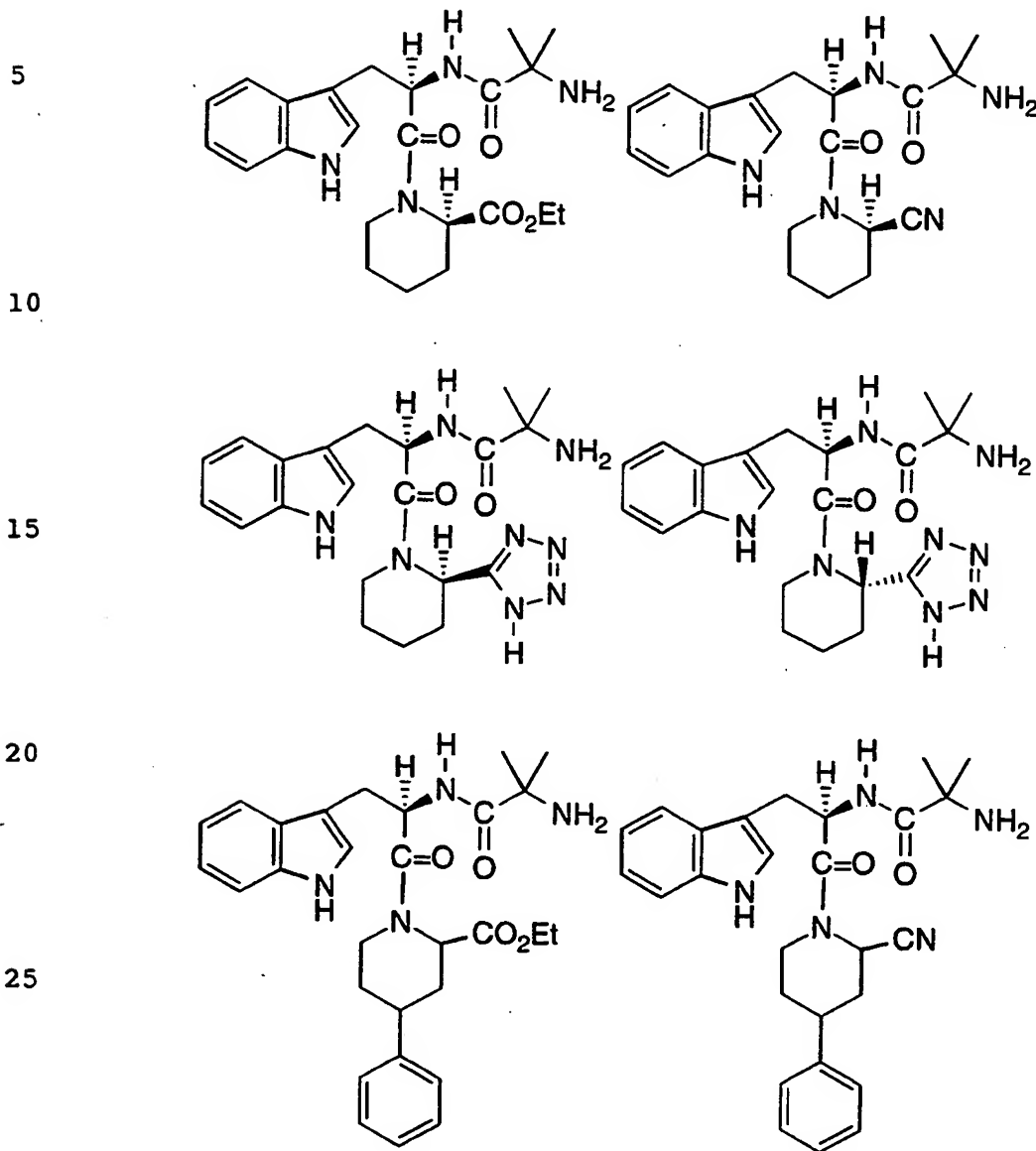


wherein R₁, R₃, R₄, R₅, A, W, X, Y, and n are as defined in Claim 2.

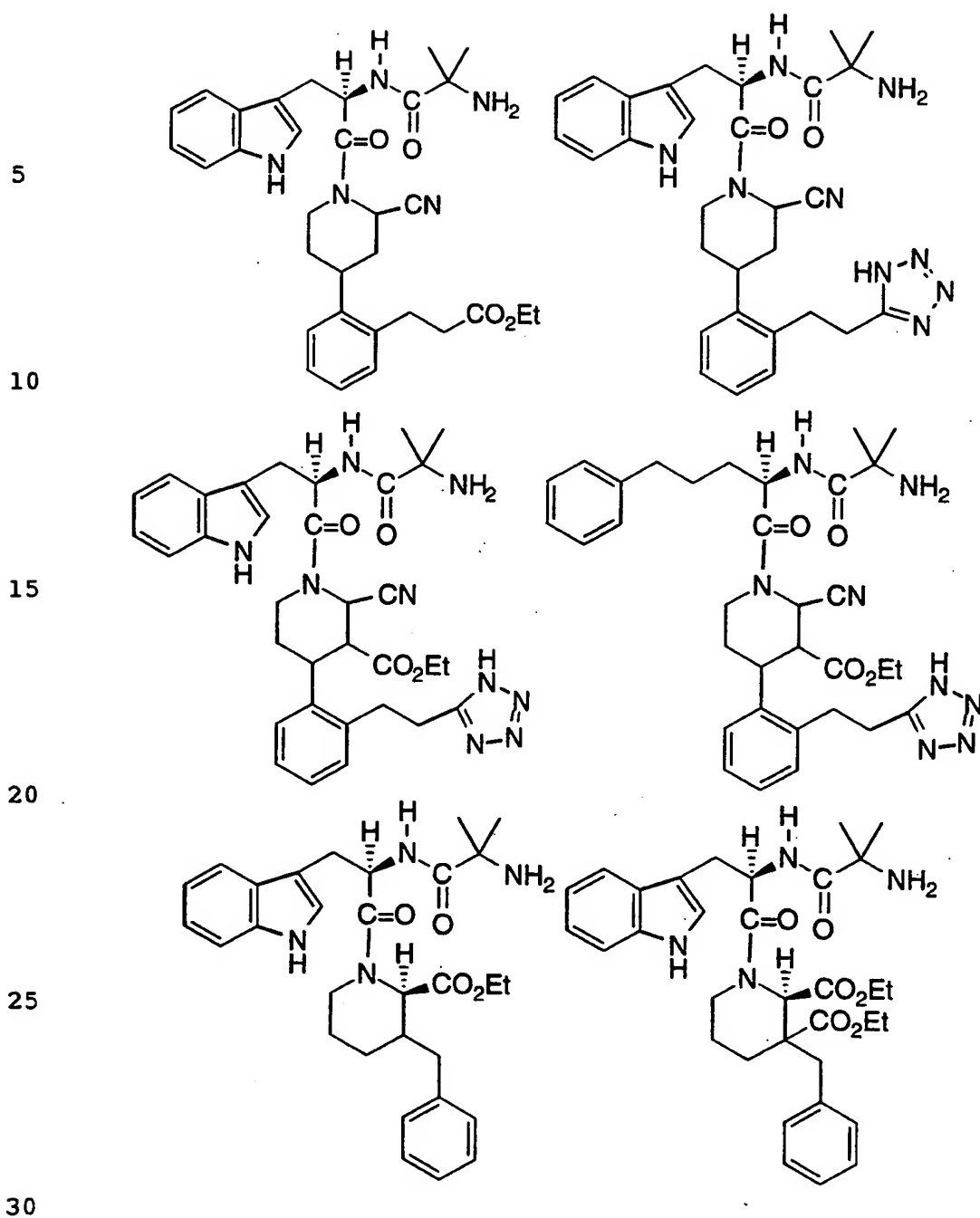
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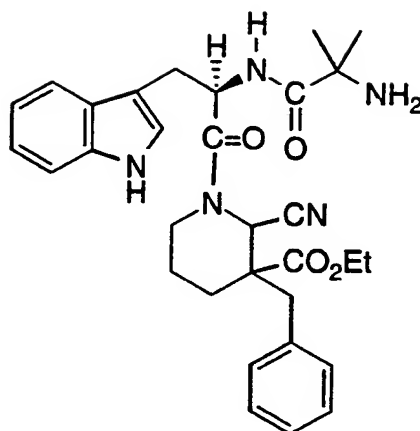
6. The compound of Claim 2 which is selected from the group consisting of:



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5

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and pharmaceutically acceptable salts and individual diastereomers thereof.

15

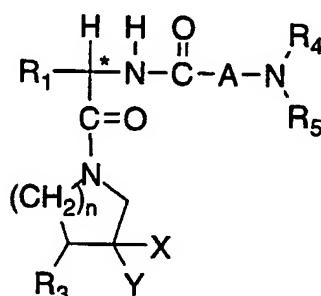
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7. A compound of the formula:



Formula BI

wherein:

R₁ is selected from the group consisting of:

C₁-C₁₀ alkyl, aryl, aryl(C₁-C₆ alkyl), (C₃-C₇ cycloalkyl)(C₁-C₆ alkyl)-,

(C₁-C₅ alkyl)-K-(C₁-C₅ alkyl)-, aryl(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-,

and (C₃-C₇ cycloalkyl)(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, where K is O, S(O)_m, N(R₂)C(O), C(O)N(R₂), OC(O), C(O)O, -CR₂=CR₂-, or -C≡C-,

where aryl is selected from: phenyl, naphthyl, indolyl, azaindole,

pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl, and

R₂ and alkyl may be further substituted by 1 to 9 halogen, S(O)_mR_{2a}, 1

to 3 of OR_{2a} or C(O)OR_{2a}, and aryl may be further substituted by 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of OR₂, methylenedioxy,

-S(O)_mR₂, 1 to 2 of -CF₃, -OCF₃, nitro, -N(R₂)C(O)(R₂), -C(O)OR₂,

-C(O)N(R₂)(R₂), -1H-tetrazol-5-yl, -SO₂N(R₂)(R₂), -N(R₂)SO₂ phenyl, or -N(R₂)SO₂R₂;

R₂ is selected from: hydrogen, C₁-C₆ alkyl, and C₃-C₇ cycloalkyl, and

where two C₁-C₆ alkyl groups are present on one atom, they may be

optionally joined to form a C₃-C₈ cyclic ring, optionally including

oxygen, sulfur or NR_{3a}, where R_{3a} is hydrogen, or C₁-C₆ alkyl,

optionally substituted by hydroxyl;

R_{2a} is hydrogen, or C₁-C₆ alkyl optionally substituted by hydroxyl;

R₃ is selected from: -(CH₂)_rphenyl, -(CH₂)_rnaphthyl, -C₁-C₁₀ alkyl,

-C₃-C₇ cycloalkyl, and the phenyl, naphthyl and C₃-C₇ cycloalkyl rings

may be substituted by 1 to 3 substituents selected from the group

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consisting of: C₁-C₆ alkyl, halogen, -OR₂, -NHSO₂CF₃, -(CH₂)_rOR₆,
 -(CH₂)_rN(R₂)(R₆), -(CH₂)_r(R₆), -(CH₂)_rC(O)OR₂, -(CH₂)_rC(O)OR₆,
 -(CH₂)_rOC(O)R₂, -(CH₂)_rOC(O)R₆, -(CH₂)_rC(O)R₂, -(CH₂)_rC(O)R₆,
 -(CH₂)_rC(O)N(R₂)(R₂), -(CH₂)_rC(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)R₂
 5 -(CH₂)_rN(R₂)C(O)R₆, -(CH₂)_rN(R₆)C(O)R₂, -(CH₂)_rN(R₆)C(O)R₆,
 -(CH₂)_rN(R₂)C(O)OR₂, -(CH₂)_rN(R₂)C(O)OR₆,
 -(CH₂)_rN(R₆)C(O)OR₂, -(CH₂)_rN(R₆)C(O)OR₆,
 -(CH₂)_rN(R₂)C(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)N(R₂)(R₂),
 -(CH₂)_rN(R₆)C(O)N(R₂)(R₆), (CH₂)_rN(R₂)SO₂R₆,
 10 -(CH₂)_rN(R₂)SO₂R₂, -(CH₂)_rN(R₆)SO₂R₂, (CH₂)_rN(R₆)SO₂R₆,
 -(CH₂)_rOC(O)N(R₂)(R₆), -(CH₂)_rOC(O)N(R₂)(R₂),
 -(CH₂)_rSO₂N(R₂)(R₆), -(CH₂)_rSO₂N(R₂)(R₂), (CH₂)_rSO₂NHC(O)R₆,
 -(CH₂)_rSO₂NHC(O)R₂, -(CH₂)_rSO₂NHC(O)OR₆,
 -(CH₂)_rSO₂NHC(O)OR₂, -(CH₂)_rC(O)NHC(O)NR₂,
 15 -(CH₂)_rC(O)NHC(O)NR₆, -(CH₂)_rC(O)NHC(O)R₂,
 -(CH₂)_rCONHC(O)R₆, -(CH₂)_rCONHSO₂R₆, -(CH₂)_rCONHSO₂R₂,
 -(CH₂)_rCONHSO₂N(R₂)(R₂), -(CH₂)_rCONHSO₂N(R₂)(R₆),
 -(CH₂)_rN(R₂)SO₂N(R₂)(R₆), -(CH₂)_rN(R₆)SO₂N(R₂)(R₆),
 -(CH₂)_rS(O)_mR₆, and -(CH₂)_rS(O)_mR₂;

20

R_{3a} is hydrogen, or C₁-C₆ alkyl optionally substituted by hydroxyl;

X is selected from: hydrogen, -C≡N, -(CH₂)_qN(R₂)C(O)R₂,
 -(CH₂)_qN(R₂)C(O)(CH₂)_taryl, -(CH₂)_qN(R₂)SO₂(CH₂)_taryl,
 25 -(CH₂)_qN(R₂)SO₂R₂, -(CH₂)_qN(R₂)C(O)N(R₂)(CH₂)_taryl,
 -(CH₂)_qN(R₂)C(O)N(R₂)(R₂), -(CH₂)_qC(O)N(R₂)(R₂),
 -(CH₂)_qC(O)N(R₂)(CH₂)_taryl, -(CH₂)_qC(O)OR₂,
 -(CH₂)_qC(O)O(CH₂)_taryl, -(CH₂)_qOR₂, -(CH₂)_qOC(O)R₂,
 -(CH₂)_qOC(O)(CH₂)_taryl, -(CH₂)_qOC(O)N(R₂)(CH₂)_taryl,
 30 -(CH₂)_qOC(O)N(R₂)(R₂), -(CH₂)_qC(O)R₂, -(CH₂)_qC(O)(CH₂)_taryl,
 -(CH₂)_qN(R₂)C(O)OR₂, -(CH₂)_qN(R₂)SO₂N(R₂)(R₂),
 -(CH₂)_qS(O)_mR₂, and -(CH₂)_qS(O)_m(CH₂)_taryl, where an R₂, (CH₂)_q
 and (CH₂)_t group may be optionally substituted by 1 to 2 C₁-C₄ alkyl,
 hydroxyl, C₁-C₄ lower alkoxy, carboxyl, CONH₂, S(O)_mCH₃,

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carboxylate C₁-C₄ alkyl esters, or 1H-tetrazol-5-yl, and aryl is phenyl, naphthyl, pyridyl, thiazolyl, or 1H-tetrazol-5-yl groups which may be optionally substituted by 1 to 3 halogen, 1 to 3 -OR₂, -CON(R₂)(R₂), -C(O)OR₂, 1 to 3 C₁-C₄ alkyl, -S(O)_mR₂, or 1H-tetrazol-5-yl;

5

Y is selected from: hydrogen, C₁-C₁₀ alkyl, -(CH₂)_taryl, -(CH₂)_q(C₃-C₇ cycloalkyl), -(CH₂)_q-K-(C₁-C₆ alkyl), -(CH₂)_q-K-(CH₂)_taryl, -(CH₂)_q-K-(CH₂)_t(C₃-C₇ cycloalkyl containing O, NR₂, S), and -(CH₂)_q-K-(CH₂)_t(C₃-C₇ cycloalkyl), where K is O, S(O)_m, C(O)NR₂, CH=CH, C≡C, N(R₂)C(O), C(O)NR₂, C(O)O, or OC(O), and where the alkyl, R₂, (CH₂)_q and (CH₂)_t groups may be optionally substituted by C₁-C₄ alkyl, hydroxyl, C₁-C₄ lower alkoxy, carboxyl, -CONH₂ or carboxylate C₁-C₄ alkyl esters, and aryl is phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiopheneyl, quinolinyl, pyrazinyl, or isothiazolyl which is optionally substituted by 1 to 3 halogen, 1 to 3 -OR₂, 1 to 2 -N(R₂)(R₂), -C(O)OR₂, -C(O)N(R₂)(R₂), nitro, -NHC(O)R₂, cyano, benzyl, 1 to 3 C₁-C₄ alkyl, -S(O)_mR₂, or 1H-tetrazol-5-yl;

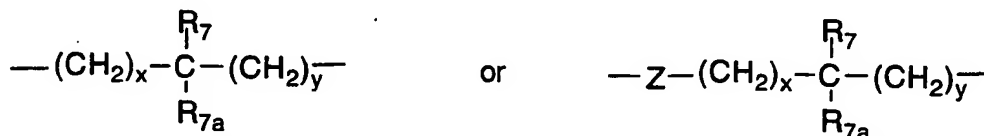
20

R₄ and R₅ are independently hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C₁-C₁₀ alkanoyloxy, 1 to 3 C₁-C₆ alkoxy, phenyl, phenoxy, 2-furyl, C₁-C₆ alkoxy carbonyl, S(O)_m(C₁-C₆ alkyl); or R₄ and R₅ can be taken together to form -(CH₂)_dL_a(CH₂)_e where L_a is C(R₂)₂, O, S(O)_m or N(R₂), d and e are independently 1 to 3 and R₂ is as defined above;

25

A is:

30



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where x and y are independently 0, 1, 2 or 3;

Z is N-R_{6a} or O, where R_{6a} is hydrogen or C₁-C₆ alkyl;

5 R₆ is hydrogen, C₁-C₆ alkyl, or (CH₂)_varyl, wherein the alkyl and (CH₂)_v groups may be optionally substituted by 1-2 O(R₂), S(O)_mR₂, 1H-tetrazol-5-yl, C(O)OR₂, C(O)N(R₂)(R₂) or SO₂N(R₂)(R₂), N(R₂)C(O)N(R₂)(R₂), and wherein aryl is phenyl, pyridyl, 1H-tetrazol-5-yl, triazolyl, imidazolyl, thiazolyl, pyrazolyl, thiadiazolyl, imidazolone-10 1-yl, oxadiazolyl, benzimidazol-2-yl, triazolinone-yl, optionally substituted with C₁-C₆ alkyl, C₃-C₆ cycloalkyl, amino, or hydroxyl;

R₇ and R_{7a} are independently hydrogen, C₁-C₆ alkyl, trifluoromethyl, phenyl, substituted C₁-C₆ alkyl where the substituents are imidazolyl, 15 phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)_mR₂, C(O)OR₂, C₃-C₇ cycloalkyl, N(R₂)(R₂), C(O)N(R₂)(R₂); or R₇ and R_{7a} can independently be joined to one or both of R₄ and R₅ groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R₇ or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms; 20 or R₇ and R_{7a} can be joined to one another to form a C₃-C₇ cycloalkyl;

m is 0, 1, or 2;

n is 1, 2, or 3;

q is 0, 1, 2, 3 or 4;

25 r is 0, 1, 2, or 3;

t is 0, 1, 2, or 3;

v is 0, 1, or 2 ;

and pharmaceutically acceptable salts and individual diastereomers thereof.

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8. The compound of Claim 7 wherein:

R₁ is selected from the group consisting of:

5 C₁-C₁₀ alkyl, aryl (C₁-C₄ alkyl)-, C₃-C₆ cycloalkyl (C₁-C₄ alkyl)-, (C₁-C₄ alkyl)-K-(C₁-C₂ alkyl)-, aryl (C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-, and (C₃-C₇ cycloalkyl)(C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-, where K is O, S(O)_m, OC(O), or C(O)O, and the alkyl groups may be further substituted by 1 to 7 halogen, S(O)_mR₂, 1 to 3 OR₂ or C(O)OR₂, and aryl is phenyl, naphthyl, indolyl, pyridyl, benzimidazolyl, azaindoleyl, 10 benzothienyl or benzofuranyl which may be further substituted by 1-2 C₁-C₄ alkyl, 1 to 2 halogen, 1 to 2 -OR₂, -S(O)_mR₂, or -C(O)OR₂;

R₂ is hydrogen, C₁-C₆ alkyl, C₃-C₇ cycloalkyl and where two C₁-C₆ alkyl groups are present on one atom they may be optionally joined to 15 form a C₄-C₇ cyclic ring optionally including oxygen, sulfur or NR_{3a};

R₃ is phenyl which is optionally substituted by 1 to 2 C₁-C₆ alkyl groups, 1 to 2 halogen, or 1 to 2 -OR₂, and which may be further substituted in the ortho position by a substituent selected from the group 20 consisting of:

-NHSO₂CF₃, -(CH₂)_rOR₆, -(CH₂)_rN(R₂)(R₆), -(CH₂)_r(R₆),
 -(CH₂)_rC(O)OR₂, -(CH₂)_rC(O)OR₆, -(CH₂)_rOC(O)R₂,
 -(CH₂)_rOC(O)R₆, -(CH₂)_rC(O)R₂, -(CH₂)_rC(O)R₆,
 -(CH₂)_rC(O)N(R₂)(R₂), -(CH₂)_rC(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)R₂
 25 -(CH₂)_rN(R₂)C(O)R₆, -(CH₂)_rN(R₆)C(O)R₂, -(CH₂)_rN(R₆)C(O)R₆,
 -(CH₂)_rN(R₂)C(O)OR₂, -(CH₂)_rN(R₂)C(O)OR₆,
 -(CH₂)_rN(R₆)C(O)OR₂, -(CH₂)_rN(R₆)C(O)OR₆,
 -(CH₂)_rN(R₂)C(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)N(R₂)(R₂),
 -(CH₂)_rN(R₆)C(O)N(R₂)(R₆), (CH₂)_rN(R₂)SO₂R₆,
 30 -(CH₂)_rN(R₂)SO₂R₂, -(CH₂)_rN(R₆)SO₂R₂, (CH₂)_rN(R₆)SO₂R₆,
 -(CH₂)_rOC(O)N(R₂)(R₆), -(CH₂)_rOC(O)N(R₂)(R₂),
 -(CH₂)_rSO₂N(R₂)(R₆), -(CH₂)_rSO₂N(R₂)(R₂), (CH₂)_rSO₂NHC(O)R₆,
 -(CH₂)_rSO₂NHC(O)R₂, -(CH₂)_rSO₂NHC(O)OR₆,
 -(CH₂)_rSO₂NHC(O)OR₂, -(CH₂)_rC(O)NHC(O)NR₂,

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$-(CH_2)_rC(O)NHC(O)NR_6$, $-(CH_2)_rC(O)NHC(O)R_2$,
 $-(CH_2)_rCONHC(O)R_6$, $-(CH_2)_rCONHSO_2R_6$, $-(CH_2)_rCONHSO_2R_2$,
 $-(CH_2)_rCONHSO_2N(R_2)R_2$, $-(CH_2)_rCONHSO_2N(R_2)R_6$,
 $-(CH_2)_rN(R_2)SO_2N(R_2)R_6$, $-(CH_2)_rN(R_6)SO_2N(R_2)R_6$,
 $-(CH_2)_rS(O)_mR_6$, and $-(CH_2)_rS(O)_mR_2$;

R_{3a} is hydrogen, or C1-C4 alkyl;

X is selected from: hydrogen, $-(CH_2)_qN(R_2)C(O)R_2$,
 $-(CH_2)_qN(R_2)C(O)(CH_2)_t\text{aryl}$, $-(CH_2)_qN(R_2)C(O)OR_2$,
 $-(CH_2)_qN(R_2)SO_2(CH_2)_t\text{aryl}$, $-(CH_2)_qN(R_2)SO_2R_2$,
 $-(CH_2)_qN(R_2)C(O)N(R_2)(CH_2)_t\text{aryl}$, $-(CH_2)_qN(R_2)C(O)N(R_2)(R_2)$,
 $-(CH_2)_qC(O)N(R_2)(R_2)$, $-(CH_2)_qC(O)N(R_2)(CH_2)_t\text{aryl}$,
 $-(CH_2)_qC(O)OR_2$, $-(CH_2)_qC(O)O(CH_2)_t\text{aryl}$, $-(CH_2)_qOC(O)R_2$,
 $-(CH_2)_qOC(O)(CH_2)_t\text{aryl}$, $-(CH_2)_qS(O)_mR_2$, and
 $-(CH_2)_qS(O)_m(CH_2)_t\text{aryl}$, where an R_2 group may be optionally
 substituted by hydroxyl, carboxyl, $CONH_2$, $S(O)_mCH_3$, carboxylate C1-
 C4 alkyl esters, or tetrazole and the aryl which is phenyl, naphthyl,
 pyridyl or 1-H-tetrazolyl may be optionally substituted by 1 to 2 halogen,
 1 to 2 $-OR_2$, $-CONH_2$, $-C(O)OR_2$, 1 to 3 C1-C4 alkyl, $-S(O)_mR_2$, or 1H-
 tetrazole-5-yl;

Y is selected from: hydrogen, C1-C8 alkyl, $(CH_2)_t\text{aryl}$, $-(CH_2)_q(C_5-C_6$
 cycloalkyl), $-(CH_2)_q-K-(C_1-C_6\text{ alkyl})$, $-(CH_2)_q-K-(CH_2)_t\text{aryl}$,
 $-(CH_2)_q-K-(CH_2)_t(C_3-C_7\text{ cycloalkyl containing O, } NR_2, \text{ or S})$, and
 $-(CH_2)_q-K-(CH_2)_t(C_5-C_6\text{ cycloalkyl})$, where K is O or $S(O)_m$ and
 where the alkyl groups may be optionally substituted by hydroxyl,
 carboxyl, $CONH_2$, carboxylate C1-C4 alkyl esters or 1H-tetrazole-5-yl
 and the aryl which is phenyl, naphthyl, pyridyl, 1-H-tetrazolyl, thiazolyl,
 imidazolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl or
 thiophenyl is optionally substituted by 1 to 3 halogen, 1 to 3 $-OR_2$, 1 to
 2 $-N(R_2)(R_2)$, $-C(O)OR_2$, $-C(O)N(R_2)(R_2)$, cyano, 1 to 2 C1-C4 alkyl,
 benzyl, $-S(O)_mR_2$, or 1H-tetrazol-5-yl;

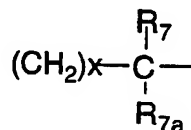
- 379 -

R4 and R5 are independently hydrogen, C1-C6 alkyl, or substituted C1-C6 alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxyl, S(O)_m (C1-C6 alkyl) or phenyl;

- 5 R6 is H, C1-C6 alkyl, or (CH₂)_varyl, wherein the (CH₂)_v and alkyl groups may be optionally substituted by 1-2 O(R₂), S(O)_mR₂, C(O)OR₂, C(O)N(R₂)(R₂) or SO₂N(R₂)(R₂), N(R₂)C(O)N(R₂)(R₂), wherein the aryl group could be phenyl, pyridyl, 1H-tetrazol-5-yl, triazolyl, imidazolyl, thiazolyl, oxadiazolyl, pyrazolyl, thiadiazolyl, benzimidazol-
10 2-yl, optionally substituted with C1-C6 alkyl, C3-C6 cycloalkyl, amino, or hydroxyl;

A is:

15



where x is 0, or 1;

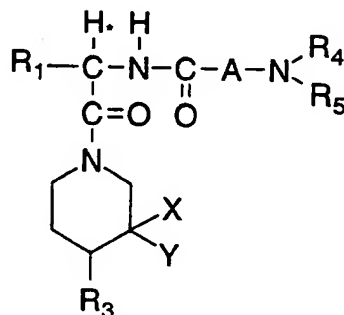
- 20 R7 and R7_a are independently hydrogen, C1-C6 alkyl, trifluoromethyl, phenyl, substituted C1-C6 alkyl where the substituents are imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)_mR₂, C(O)OR₂, C5-C7 cycloalkyl, N(R₂)(R₂), C(O)N(R₂)(R₂); or R7 and R7_a can
25 independently be joined to one of R4 or R5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of R7 or R7_a groups to form 5 or 6 membered rings; or R7 and R7_a can be joined to one another to form a C3 cycloalkyl;

- 30 n is 2;
m is 0, 1, or 2;
r is 0, 1, 2, or 3;
q is 0, 1, 2, or 3;
t is 0, 1, 2, or 3;
v is 0, 1, or 2,

- 380 -

and pharmaceutically acceptable salts and individual diastereomers thereof.

9. The compound of Claim 7 of the formula:



Formula BIb

wherein:

R₁ is selected from the group consisting of: C₁-C₁₀ alkyl, aryl (C₁-C₃ alkyl)-, (C₃-C₇ cycloalkyl)(C₁-C₃ alkyl)-, and aryl (C₀-C₁ alkyl)-K-(C₁-C₂ alkyl)-, where K is O or S(O)_m and aryl is specifically phenyl, pyridyl, naphthyl, indolyl, azaindolyl, or benzimidazolyl which is optionally substituted by 1-2 C₁-C₄ alkyl, 1 to 2 halogen, 1 to 2 OR₂, S(O)_m R₂, or C(O)OR₂;

R₂ is hydrogen, C₁-C₆ alkyl, C₃-C₇ cycloalkyl and where two C₁-C₆ alkyl groups are present on one atom they may be optionally joined to form a C₅-C₇ cyclic ring optionally including oxygen, sulfur or NR_{3a};

R₃ is phenyl optionally substituted by 1 to 2 C₁-C₆ alkyl groups, 1 to 2 halogen or 1 to 2 OR₂, and which may be further substituted in the ortho position by a substituent selected from the group consisting of:

-NH₂SO₂CF₃, -(CH₂)_rOR₆, -(CH₂)_rN(R₂)(R₆), -(CH₂)_r(R₆), -(CH₂)_rC(O)OR₆, -(CH₂)_rOC(O)R₂, -(CH₂)_rOC(O)R₆, -(CH₂)_rC(O)R₂, -(CH₂)_rC(O)R₆, -(CH₂)_rC(O)N(R₂)(R₂), -(CH₂)_rC(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)R₂, -(CH₂)_rN(R₂)C(O)R₆, -(CH₂)_rN(R₆)C(O)R₂, -(CH₂)_rN(R₆)C(O)R₆, -(CH₂)_rN(R₂)C(O)OR₂,

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$-(CH_2)_rN(R_2)C(O)OR_6$, $-(CH_2)_rN(R_6)C(O)OR_2$,
 $-(CH_2)_rN(R_6)C(O)OR_6$, $-(CH_2)_rN(R_2)C(O)N(R_2)(R_6)$,
 $-(CH_2)_rN(R_2)C(O)N(R_2)(R_2)$, $-(CH_2)_rN(R_6)C(O)N(R_2)(R_6)$,
 $(CH_2)_rN(R_2)SO_2R_6$, $-(CH_2)_rN(R_2)SO_2R_2$, $-(CH_2)_rN(R_6)SO_2R_2$,
5 $CH_2)_rN(R_6)SO_2R_6$, $-(CH_2)_rOC(O)N(R_2)(R_6)$,
 $-(CH_2)_rOC(O)N(R_2)(R_2)$, $-(CH_2)_rSO_2N(R_2)(R_6)$,
 $-(CH_2)_rSO_2N(R_2)(R_2)$, $(CH_2)_rSO_2NHC(O)R_6$, $-(CH_2)_rSO_2NHC(O)R_2$,
 $-(CH_2)_rSO_2NHC(O)OR_6$, $-(CH_2)_rSO_2NHC(O)OR_2$,
 $-(CH_2)_rCONHSO_2R_6$, $-(CH_2)_rCONHSO_2R_2$, $-(CH_2)_rS(O)_mR_6$, and
10 $-(CH_2)_rS(O)_mR_2$;

R_{3a} is hydrogen, or C₁-C₄ alkyl;

X is selected from: hydrogen, $-(CH_2)_qN(R_2)C(O)R_2$,
15 $-(CH_2)_qN(R_2)C(O)(CH_2)_t\text{aryl}$, $-(CH_2)_qN(R_2)SO_2(CH_2)_t\text{aryl}$, $-(CH_2)_qN(R_2)SO_2R_2$, $-(CH_2)_qN(R_2)C(O)N(R_2)(CH_2)_t\text{aryl}$,
 $-(CH_2)_qN(R_2)C(O)N(R_2)(R_2)$, $-(CH_2)_qC(O)N(R_2)(R_2)$,
 $-(CH_2)_qN(R_2)C(O)OR_2$, $-(CH_2)_qC(O)N(R_2)(CH_2)_t\text{aryl}$,
 $-(CH_2)_qC(O)OR_2$, $-(CH_2)_qC(O)O(CH_2)_t\text{aryl}$, $-(CH_2)_qOC(O)R_2$,
20 $-(CH_2)_qOC(O)(CH_2)_t\text{aryl}$, $-(CH_2)_qS(O)_mR_2$, and
 $-(CH_2)_qS(O)_m(CH_2)_t\text{aryl}$, where an R_2 group may be optionally
substituted by hydroxyl, carboxyl, $-CONH_2$, $-S(O)_mCH_3$, carboxylate
C₁-C₄ alkyl esters or tetrazole and aryl is phenyl, naphthyl or pyridyl
which may be further substituted by 1-2 halogen, 1 to 2 OR_2 , $C(O)OR_2$,
25 1 to 3 C₁-C₄ alkyl, $S(O)_mR_2$, or 1H-tetrazole-5-yl;

Y is selected from: hydrogen, C₁-C₈ alkyl, $(CH_2)_t\text{aryl}$, $-(CH_2)_qC_5-C_7$
cycloalkyl, $-(CH_2)_q-K-(C_1-C_6\text{ alkyl})$, $-(CH_2)_q-K-(CH_2)_t\text{aryl}$, and
 $-(CH_2)_q-K-(CH_2)_t$ (C₅-C₆ cycloalkyl), where K is $S(O)_m$ and where the
30 alkyl groups may be optionally substituted by hydroxyl, carboxyl,
 $CONH_2$, carboxylate C₁-C₄ alkyl esters or 1H-tetrazole-5-yl and aryl is
specifically phenyl, naphthyl, pyridyl, thiazolyl, thiophenyl, pyrazolyl,
oxazolyl, isoxazolyl or imidazolyl which may be optionally substituted

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by 1 to 2 halogen, 1 to 2 OR₂, 1 to 2 -N(R₂)(R₂), -CO(OR₂), 1 to 2 C₁-C₄ alkyl, S(O)_mR₂, or 1H-tetrazol-5-yl;

R₄ and R₅ are independently hydrogen, C₁-C₄ alkyl, substituted C₁-C₃ alkyl where the substituents may be 1 to 2 hydroxyl;

5

R₆ is hydrogen, C₁-C₆ alkyl or (CH₂)_varyl, wherein the C₁-C₆ alkyl and the (CH₂)_varyl groups may be optionally substituted by 1-2 O(R₂),

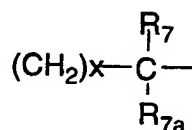
S(O)_mR₂, C(O)OR₂, C(O)N(R₂)(R₂) or SO₂N(R₂)(R₂),

10

N(R₂)C(O)N(R₂)(R₂), wherein aryl is specifically phenyl, pyridyl, 1H-tetrazol-5-yl, triazolyl, imidazolyl, thiazolyl, oxadiazolyl, pyrazolyl, thiadiazolyl, benzimidazol-2-yl, optionally substituted with C₁-C₆ alkyl, C₃-C₆ cycloalkyl, amino, or hydroxyl;

A is:

15



20 where x is 0, or 1;

R₇ and R_{7a} are independently hydrogen, C₁-C₂ alkyl, phenyl, substituted C₁-C₆ alkyl wherein the substituent is imidazolyl, phenyl, indolyl, p-

hydroxyphenyl, OR₂, S(O)_mR₂; or R₇ and R_{7a} can be independently be

25 joined to one another to form a C₃ cycloalkyl;

m is 0, 1, or 2;

r is 0, 1, 2, or 3;

q is 0, 1, 2, or 3;

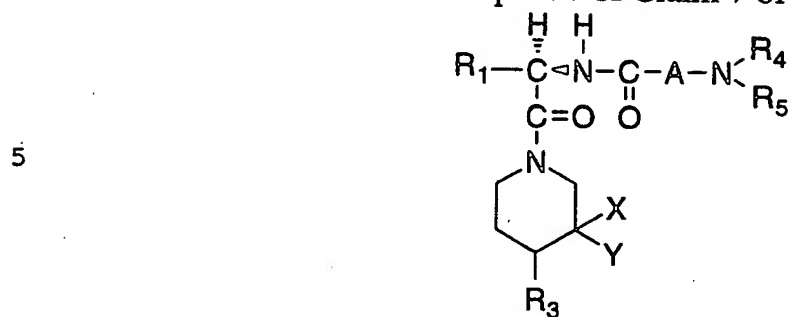
30 t is 0, 1, 2, or 3;

v is 0, 1, or 2;

and pharmaceutically acceptable salts and individual diastereomers thereof.

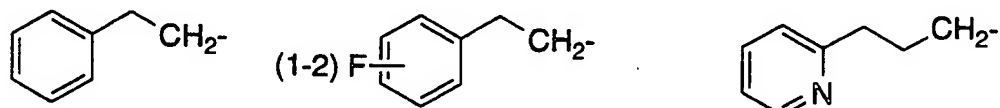
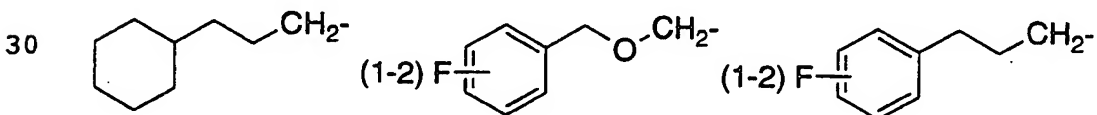
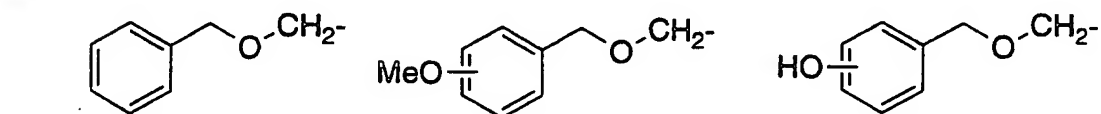
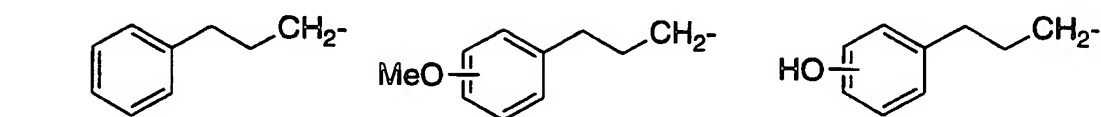
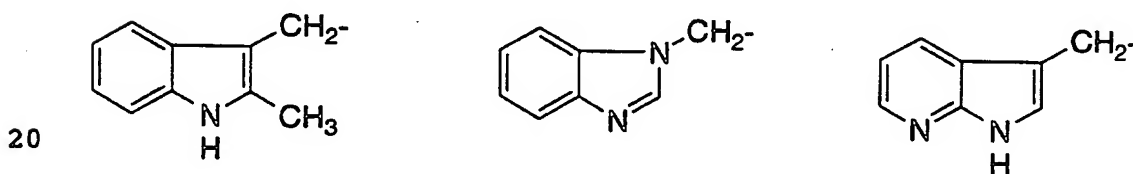
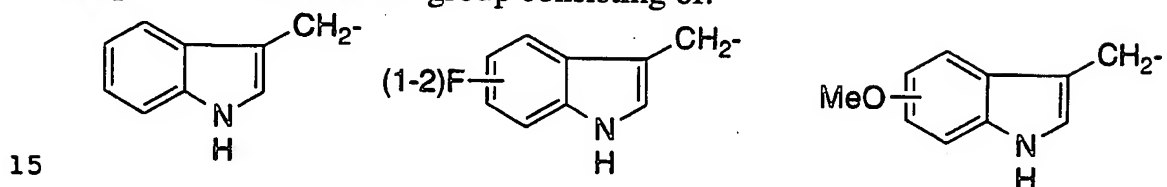
- 383 -

10. The compound of Claim 7 of the formula:



Formula BIc

10 wherein:

R₁ is selected from the group consisting of:

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or their regioisomers where not specified;

R₂ is hydrogen, C₁-C₆ alkyl, or C₃-C₇ cycloalkyl and where two C₁-C₆ alkyl groups are present on one atom they may be optionally joined to form a C₅-C₇ cyclic ring optionally including oxygen, sulfur or NR_{3a};

5

R₃ is phenyl optionally substituted in the ortho position with a substituent selected from the group consisting of:

-NHSO₂CF₃, -(CH₂)_rOR₆, -(CH₂)_r(R₆), -(CH₂)_rC(O)OR₂,
 -(CH₂)_rC(O)OR₆, -(CH₂)_rOC(O)R₂, -(CH₂)_rOC(O)R₆,
 10 -(CH₂)_rC(O)R₂, -(CH₂)_rC(O)R₆, -(CH₂)_rC(O)N(R₂)(R₂),
 -(CH₂)_rC(O)N(R₂)(R₆), -(CH₂)_rN(R₂)C(O)R₂, -(CH₂)_rN(R₂)C(O)R₆,
 -(CH₂)_rN(R₆)C(O)R₂, -(CH₂)_rN(R₆)C(O)R₆, -(CH₂)_rN(R₂)C(O)OR₂,
 -(CH₂)_rN(R₂)C(O)OR₆, -(CH₂)_rN(R₆)C(O)OR₂,
 -(CH₂)_rN(R₆)C(O)OR₆, -(CH₂)_rN(R₂)C(O)N(R₂)(R₆),
 15 -(CH₂)_rN(R₂)C(O)N(R₂)(R₂), -(CH₂)_rN(R₆)C(O)N(R₂)(R₆),
 (CH₂)_rN(R₂)SO₂R₆, -(CH₂)_rN(R₂)SO₂R₂, -(CH₂)_rN(R₆)SO₂R₂,
 (CH₂)_rN(R₆)SO₂R₆, -(CH₂)_rOC(O)N(R₂)(R₆),
 -(CH₂)_rOC(O)N(R₂)(R₂), -(CH₂)_rSO₂N(R₂)(R₆),
 -(CH₂)_rSO₂N(R₂)(R₂), (CH₂)_rSO₂NHC(O)R₆, -(CH₂)_rSO₂NHC(O)R₂,
 20 -(CH₂)_rSO₂NHC(O)OR₆, -(CH₂)_rSO₂NHC(O)OR₂,
 -(CH₂)_rCONHSO₂R₆, -(CH₂)_rCONHSO₂R₂, -(CH₂)_rS(O)_mR₆, and
 -(CH₂)_rS(O)_mR₂;

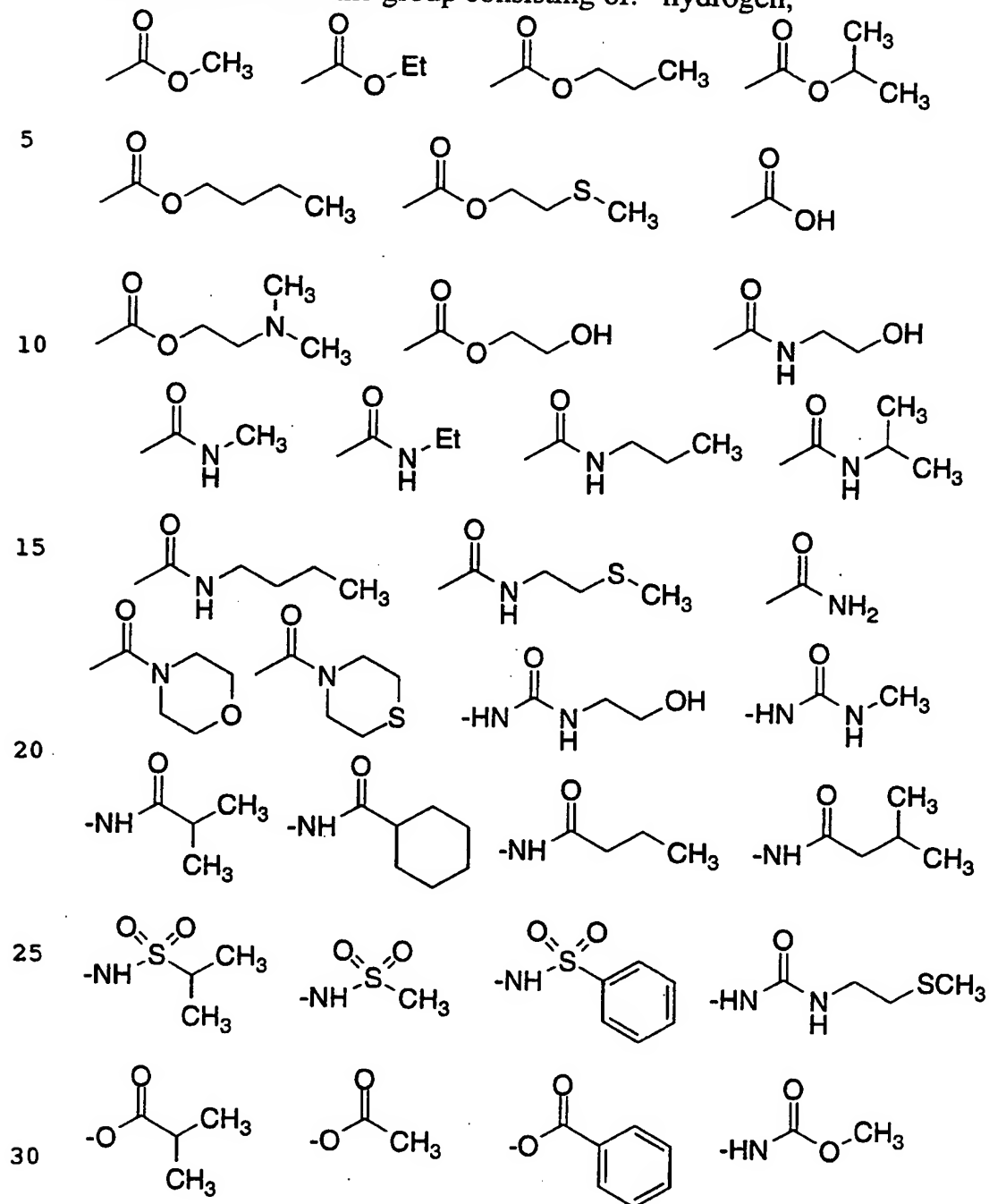
25

R_{3a} is hydrogen, or C₁-C₄ alkyl;

30

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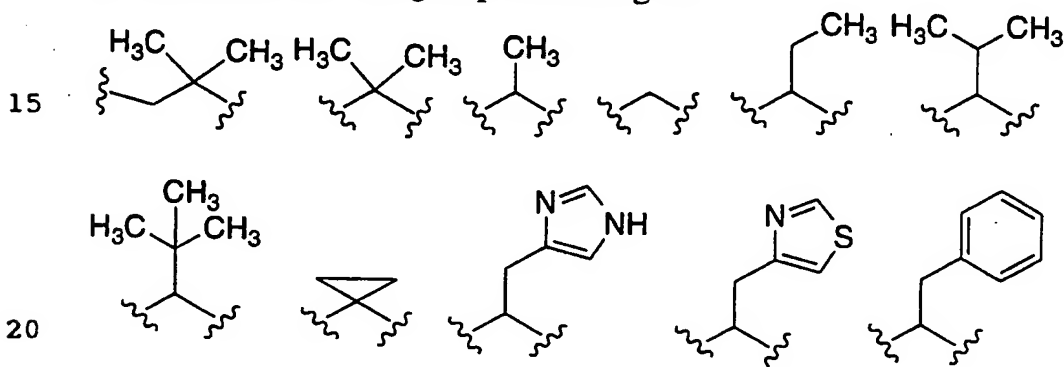
X is selected from the group consisting of: hydrogen,



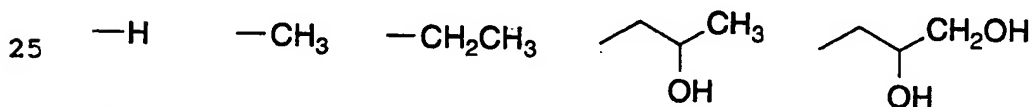
- 386 -

Y is selected from the group consisting of:
 hydrogen, C₁-C₈ alkyl, (CH₂)_taryl, -(CH₂)_q C₅-C₇ cycloalkyl, -(CH₂)_q-
 K-(C₁-C₆ alkyl), -(CH₂)_q-K-(CH₂)_taryl, or -(CH₂)_q-K-(CH₂)_t (C₅-C₆
 cycloalkyl) where K is S(O)_m and where the alkyl groups may be
 5 optionally substituted by hydroxyl, carboxyl, CONH₂, carboxylate C₁-
 C₄ alkyl esters or 1H-tetrazole-5-yl, and where aryl is specifically
 phenyl, naphthyl, pyridyl, thiazolyl, thiophenyl, pyrazolyl, oxazolyl,
 isoxazolyl, thiadiazolyl, pyrimidinyl, or imidazolyl, which may be
 optionally substituted by 1 to 2 halogen, 1 to 2 OR₂, CO(OR₂), 1 to 2
 10 C₁-C₄ alkyl, S(O)_mR₂ or 1H-tetrazol-5-yl;

A is selected from the group consisting of:

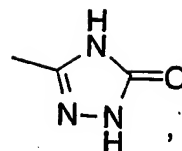
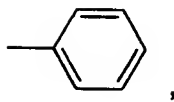
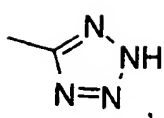


R₄ and R₅ are independently selected from the group consisting of:

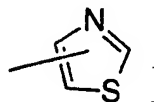
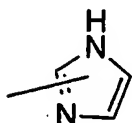


R₆ is hydrogen, C₁-C₆ alkyl or (CH₂)_varyl wherein the alkyl and
 (CH₂)_v groups may be optionally substituted by halogen, OR₂,
 N(R₂)(R₂), C₃-C₆ cycloalkyl, 1H-tetrazol-5-yl, C(O)OR₂,
 30 C(O)N(R₂)(R₂), SO₂N(R₂)(R₂) or N(R₂)C(O)N(R₂)(R₂), wherein aryl
 is selected from the following aromatic groups and their regioisomers:

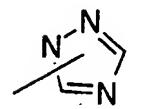
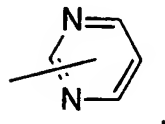
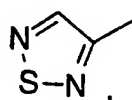
- 387 -



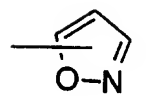
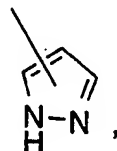
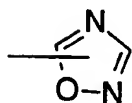
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10



15



where the aromatic groups are optionally substituted with C₁-C₂ alkyl,
 20 -N(R₂)(R₂), or hydroxy;

m is 0, 1, or 2;

r is 0, 1, 2, or 3;

q is 0 or 1;

25 t is 0 or 1;

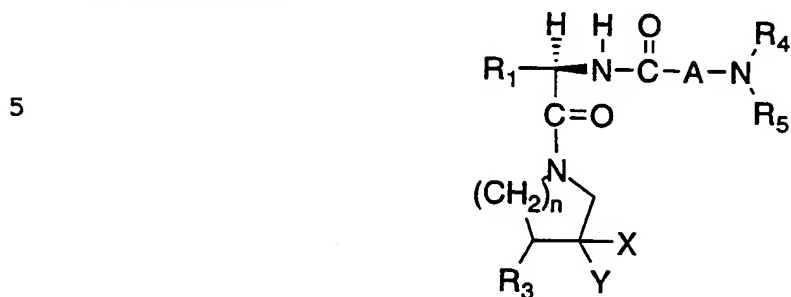
v is 0 or 1;

and pharmaceutically acceptable salts and individual diastereomers
 thereof.

30

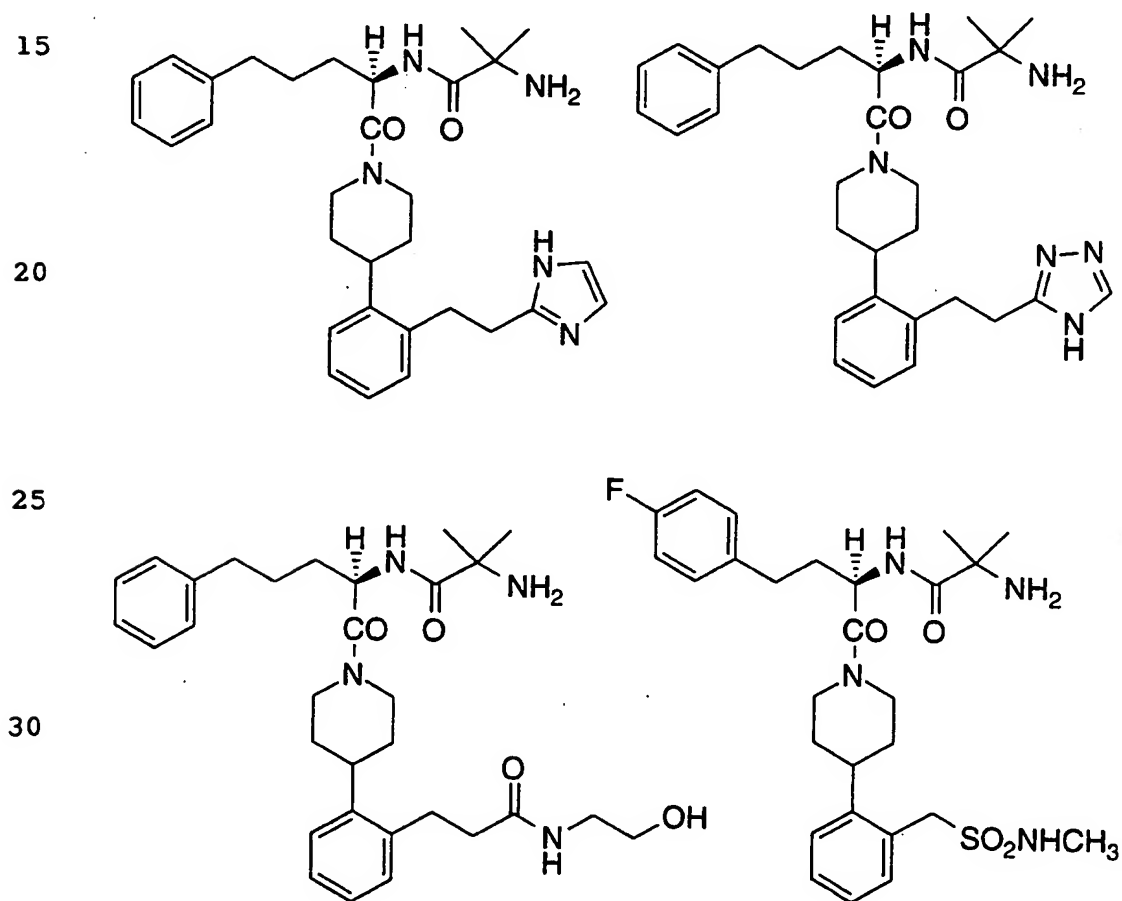
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11. The stereospecifically defined compound of Claim 7 of the formula:

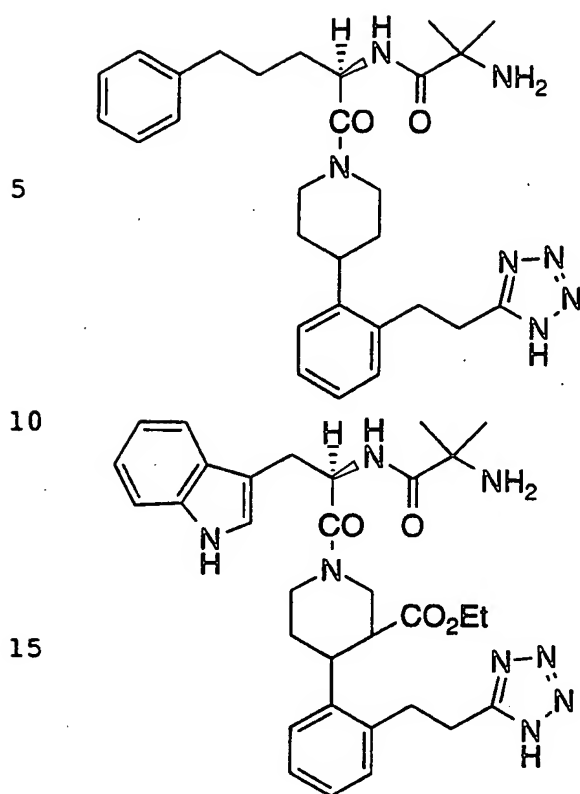


wherein R₁, R₃, R₄, R₅, A, X, Y, and n are as defined in Claim 7.

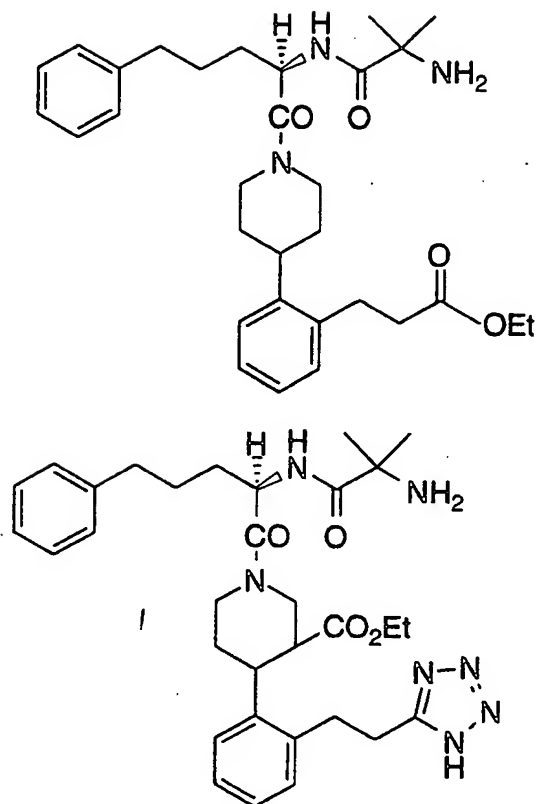
12. The compound of Claim 7 which is selected from the group consisting of:



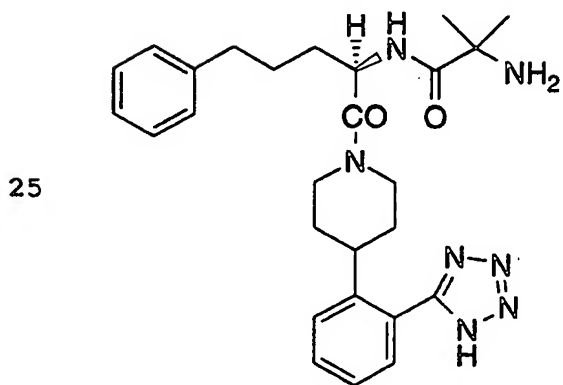
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cis d₁, cis d₂, trans d₁, trans d₂

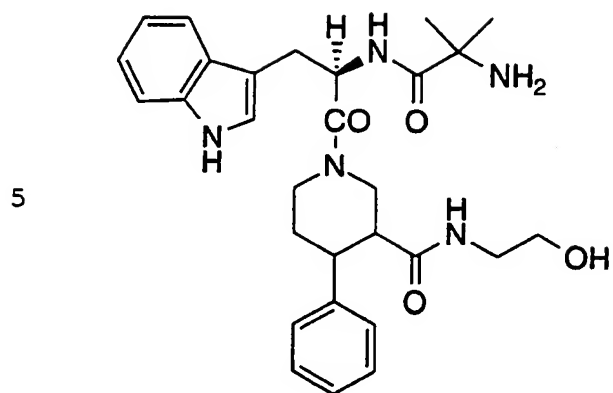


cis d₁, cis d₂, trans d₁, trans d₂

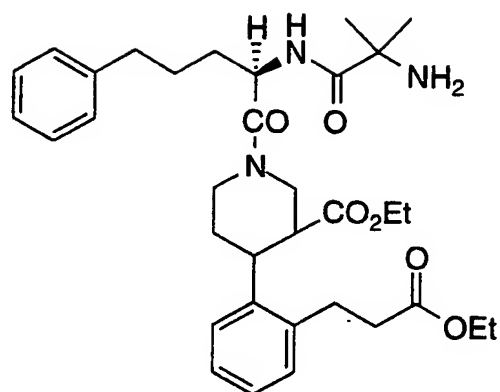


cis d₁, cis d₂, trans d₁, trans d₂

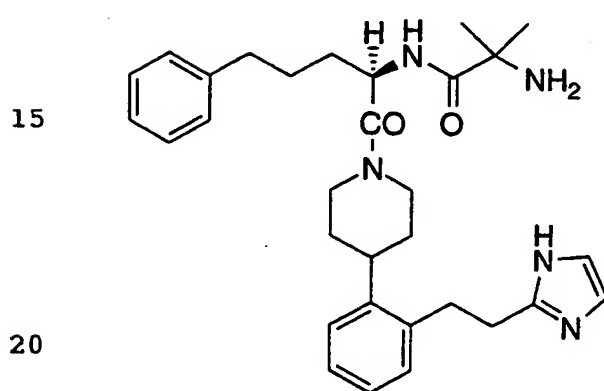
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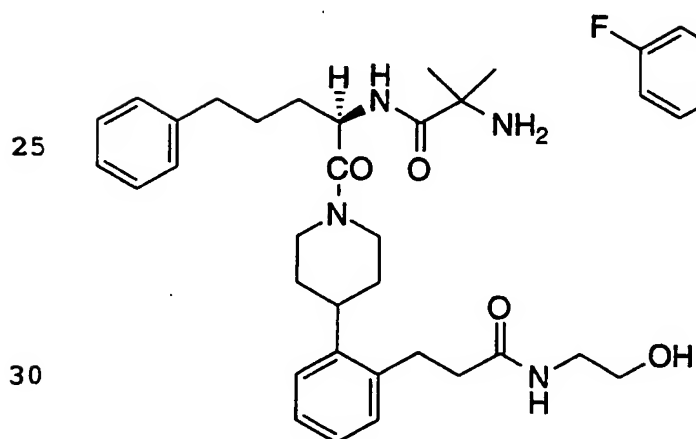
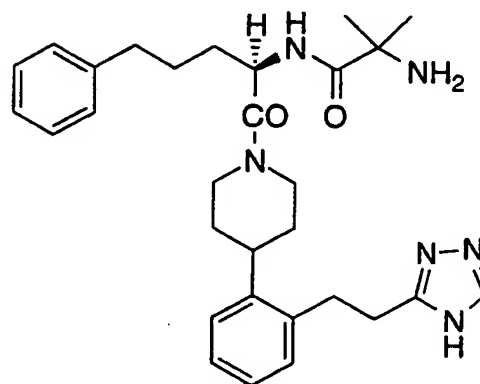
10 cis d₁, cis d₂, trans d₁, trans d₂



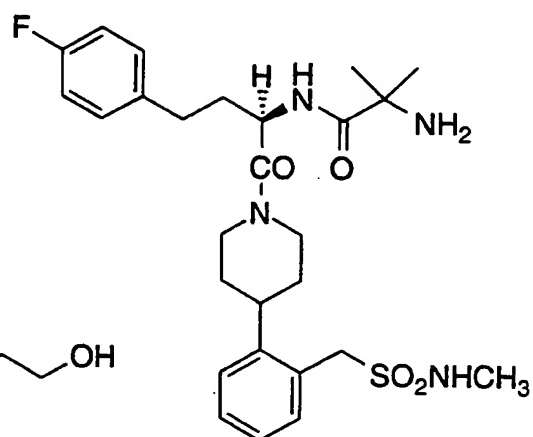
cis d₁, cis d₂, trans d₁, trans d₂



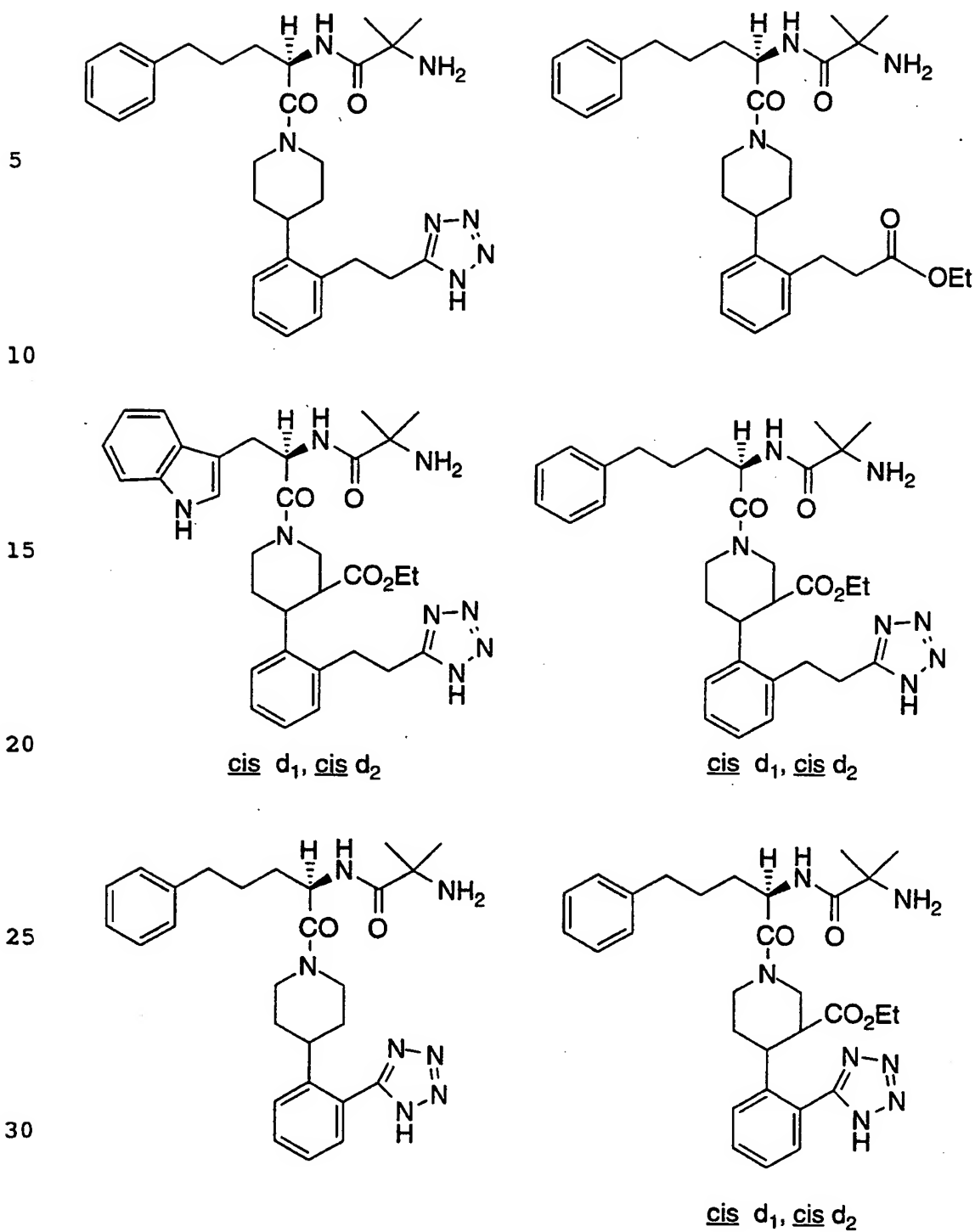
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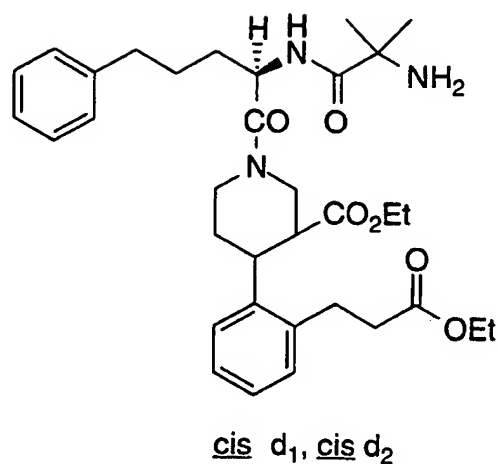
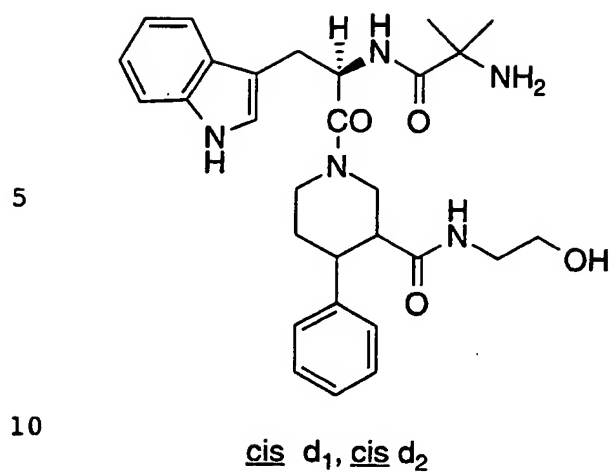
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and their pharmaceutically acceptable salts and individual diastereomers thereof where not otherwise specified.

15

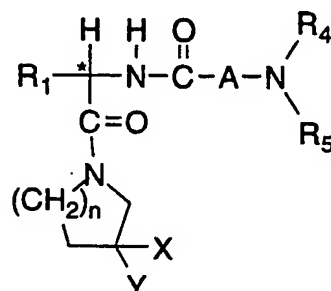
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13. A compound of the formula:



Formula CI

wherein:

R₁ is selected from the group consisting of:C₁-C₁₀ alkyl, aryl, aryl(C₁-C₆ alkyl), (C₃-C₇ cycloalkyl)(C₁-C₆ alkyl)-,(C₁-C₅ alkyl)-K-(C₁-C₅ alkyl)-, aryl(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-,

15 and (C₃-C₇ cycloalkyl)(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, where K is O, S(O)_m, N(R₂)C(O), C(O)N(R₂), OC(O), C(O)O, -CR₂=CR₂-, or -C≡C-, where aryl is selected from: phenyl, naphthyl, indolyl, azaindole,

pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl, and

20 R₂ and alkyl may be further substituted by 1 to 9 halogen, S(O)_mR_{2a}, 1 to 3 of OR_{2a} or C(O)OR_{2a}, and aryl may be further substituted by 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of OR₂, methylenedioxy, -S(O)_mR₂, 1 to 2 of -CF₃, -OCF₃, nitro, -N(R₂)C(O)(R₂), -C(O)OR₂, -C(O)N(R₂)(R₂), -1H-tetrazol-5-yl, -SO₂N(R₂)(R₂), -N(R₂)SO₂ phenyl, or -N(R₂)SO₂R₂;

25 R₂ is selected from: hydrogen, C₁-C₆ alkyl, and C₃-C₇ cycloalkyl, and where two C₁-C₆ alkyl groups are present on one atom, they may be optionally joined to form a C₃-C₈ cyclic ring, optionally including oxygen, sulfur or NR_{3a}, where R_{3a} is hydrogen, or C₁-C₆ alkyl,

30 optionally substituted by hydroxyl;

R_{2a} is hydrogen, or C₁-C₆ alkyl optionally substituted by hydroxyl;

X is selected from: hydrogen, -C≡N, -(CH₂)_qN(R₂)C(O)R₂, -(CH₂)_qN(R₂)C(O)(CH₂)_taryl, -(CH₂)_qN(R₂)SO₂(CH₂)_taryl, -(CH₂)_qN(R₂)SO₂R₂, -(CH₂)_qN(R₂)C(O)N(R₂)(CH₂)_taryl,

- 394 -

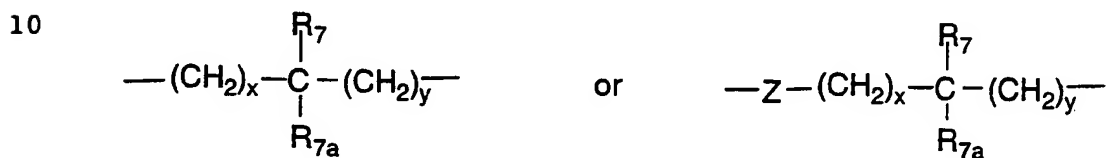
- (CH₂)_qN(R₂)C(O)N(R₂)(R₂), -(CH₂)_qC(O)N(R₂)(R₂),
 -(CH₂)_qC(O)N(R₂)(CH₂)_taryl, -(CH₂)_qC(O)OR₂,
 -(CH₂)_qC(O)O(CH₂)_taryl, -(CH₂)_qOR₂, -(CH₂)_qOC(O)R₂,
 -(CH₂)_qOC(O)(CH₂)_taryl, -(CH₂)_qOC(O)N(R₂)(CH₂)_taryl,
 5 -(CH₂)_qOC(O)N(R₂)(R₂), -(CH₂)_qC(O)R₂, -(CH₂)_qC(O)(CH₂)_taryl,
 -(CH₂)_qN(R₂)C(O)OR₂, -(CH₂)_qN(R₂)SO₂N(R₂)(R₂),
 -(CH₂)_qS(O)_mR₂, and -(CH₂)_qS(O)_m(CH₂)_taryl, where an R₂, (CH₂)_q
 and (CH₂)_t group may be optionally substituted by 1 to 2 C₁-C₄ alkyl,
 hydroxyl, C₁-C₄ lower alkoxy, carboxyl, CONH₂, S(O)_mCH₃,
 10 carboxylate C₁-C₄ alkyl esters, or 1H-tetrazol-5-yl, and aryl is phenyl,
 naphthyl, pyridyl, thiazolyl, or 1H-tetrazol-5-yl groups which may be
 optionally substituted by 1 to 3 halogen, 1 to 3 -OR₂, -CON(R₂)(R₂),
 -C(O)OR₂, 1 to 3 C₁-C₄ alkyl, -S(O)_mR₂, or 1H-tetrazol-5-yl;
- 15 Y is selected from: hydrogen, C₁-C₁₀ alkyl, -(CH₂)_taryl,
 -(CH₂)_q(C₃-C₇ cycloalkyl), -(CH₂)_q-K-(C₁-C₆ alkyl),
 -(CH₂)_q-K-(CH₂)_taryl, -(CH₂)_q-K-(CH₂)_t(C₃-C₇ cycloalkyl)
 containing O, NR₂, S), and -(CH₂)_q-K-(CH₂)_t(C₃-C₇ cycloalkyl), where
 K is O, S(O)_m, C(O)NR₂, CH=CH, C≡C, N(R₂)C(O), C(O)NR₂, C(O)O,
 20 or OC(O), and where the alkyl, R₂, (CH₂)_q and (CH₂)_t groups may be
 optionally substituted by C₁-C₄ alkyl, hydroxyl, C₁-C₄ lower alkoxy,
 carboxyl, -CONH₂ or carboxylate C₁-C₄ alkyl esters, and aryl is phenyl,
 naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl,
 25 pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiophenyl,
 quinolinyl, pyrazinyl, or isothiazolyl which is optionally substituted by 1
 to 3 halogen, 1 to 3 -OR₂, -C(O)OR₂, -C(O)N(R₂)(R₂), nitro, cyano,
 benzyl, 1 to 3 C₁-C₄ alkyl, -S(O)_mR₂, or 1H-tetrazol-5-yl, with the
 proviso that if X is hydrogen, Y is other than hydrogen;

30

- 395 -

R4 and R5 are independently hydrogen, C1-C6 alkyl, or substituted C1-C6 alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C1-C10 alkanoyloxy, 1 to 3 C1-C6 alkoxy, phenyl, phenyloxy, 2-furyl, C1-C6 alkoxy carbonyl, S(O)_m(C1-C6 alkyl), or R4 and R5 may be taken
 5 together to form -(CH₂)_d-L_a(CH₂)_e- where L_a is -C(R₂)₂-, O, S(O)_m or N(R₂), d and e are independently 1 to 3 and R₂ is as defined above;

A is:



15 where x and y are independently 0, 1, 2 or 3;

Z is N-R_{6a} or O, where R_{6a} is hydrogen or C1-C6 alkyl;

R7 and R_{7a} are independently hydrogen, C1-C6 alkyl, trifluoromethyl, phenyl, or substituted C1-C6 alkyl where the substituents are imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)_mR₂, C(O)OR₂, C3-C7
 20 cycloalkyl, N(R₂)(R₂), C(O)N(R₂)(R₂), or R7 and R_{7a} may independently be joined to one or both of R4 and R5 groups to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms, or
 25 R7 and R_{7a} can be joined to one another to form C3-C7 cycloalkyl;

m is 0, 1, or 2;

n is 1, 2, or 3;

q is 0, 1, 2, 3, or 4;

30 t is 0, 1, 2, or 3;

and pharmaceutically acceptable salts and individual diastereomers thereof.

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14. The compound of Claim 13 wherein:

R₁ is selected from the group consisting of:

C₁-C₁₀ alkyl, aryl (C₁-C₄ alkyl)-, C₃-C₆ cycloalkyl (C₁-C₄ alkyl)-, (C₁-C₄ alkyl)-K-(C₁-C₂ alkyl)-, aryl (C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-, and (C₃-C₇ cycloalkyl)(C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-, where K is O, S(O)_m, OC(O), or C(O)O, and the alkyl groups may be further substituted by 1 to 7 halogen, S(O)_mR₂, 1 to 3 OR₂ or C(O)OR₂, and aryl is phenyl, naphthyl, indolyl, pyridyl, benzimidazolyl, azaindoleyl, benzothienyl or benzofuranyl which may be further substituted by 1-2 C₁-C₄ alkyl, 1 to 2 halogen, 1 to 2 -OR₂, -S(O)_mR₂, or -C(O)OR₂;

R₂ is hydrogen, C₁-C₆ alkyl, or C₃-C₇ cycloalkyl, and where two C₁-C₆ alkyl groups are present on one atom they may be optionally joined to form a C₄-C₇ cyclic ring optionally including oxygen, sulfur or NR_{3a}; R_{3a} is hydrogen, or C₁-C₄ alkyl;

X is selected from: hydrogen, -(CH₂)_qN(R₂)C(O)R₂, -(CH₂)_qN(R₂)C(O)(CH₂)_taryl, -(CH₂)_qN(R₂)C(O)OR₂, -(CH₂)_qN(R₂)SO₂(CH₂)_taryl, -(CH₂)_qN(R₂)SO₂R₂, -(CH₂)_qN(R₂)C(O)N(R₂)(CH₂)_taryl, -(CH₂)_qN(R₂)C(O)N(R₂)(R₂), -(CH₂)_qC(O)N(R₂)(R₂), -(CH₂)_qC(O)N(R₂)(CH₂)_taryl, -(CH₂)_qC(O)OR₂, -(CH₂)_qC(O)O(CH₂)_taryl, -(CH₂)_qOC(O)R₂, -(CH₂)_qOC(O)(CH₂)_taryl, -(CH₂)_qS(O)_mR₂, and -(CH₂)_qS(O)_m(CH₂)_taryl, where an R₂ group may be optionally substituted by hydroxyl, carboxyl, CONH₂, S(O)_mCH₃, carboxylate C₁-C₄ alkyl esters, or tetrazole, and aryl is phenyl, naphthyl, pyridyl or 1-H-tetrazolyl which may be optionally substituted by 1 to 2 halogen, 1 to 2 -OR₂, -CONH₂, -C(O)OR₂, 1 to 3 C₁-C₄ alkyl, -S(O)_mR₂, or 1H-tetrazole-5-yl;

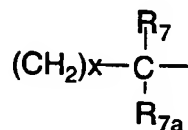
Y is selected from: hydrogen, C₁-C₈ alkyl, (CH₂)_taryl, -(CH₂)_q(C₅-C₆ cycloalkyl), -(CH₂)_q-K-(C₁-C₆ alkyl), -(CH₂)_q-K-(CH₂)_taryl, -(CH₂)_q-K-(CH₂)_t(C₃-C₇ cycloalkyl containing O, NR₂, or S), and -(CH₂)_q-K-(CH₂)_t(C₅-C₆ cycloalkyl), where K is O or S(O)_m and

- 397 -

where the alkyl groups may be optionally substituted by hydroxyl, carboxyl, CONH₂, carboxylate C₁-C₄ alkyl esters or 1H-tetrazole-5-yl and aryl is phenyl, naphthyl, pyridyl, 1-H-tetrazolyl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, or thiophenyl which is optionally substituted by 1 to 3 halogen, 1 to 3 -OR₂, -C(O)OR₂, -C(O)N(R₂)(R₂), cyano, 1 to 2 C₁-C₄ alkyl, benzyl, -S(O)_mR₂, or 1H-tetrazol-5-yl, with the proviso that if X is hydrogen, Y is other than hydrogen;

R₄ and R₅ are independently hydrogen, C₁-C₆ alkyl, or substituted C₁-C₆ alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxyl, S(O)_m (C₁-C₆ alkyl) or phenyl;

A is:



where x is 0, or 1;
R₇ and R_{7a} are independently hydrogen C₁-C₆ alkyl, trifluoromethyl, phenyl, substituted C₁-C₆ alkyl where the substituents are imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)_mR₂, C(O)OR₂, C₅-C₇ cycloalkyl, -N(R₂)(R₂), -C(O)N(R₂)(R₂); or R₇ and R_{7a} can independently be joined to one of R₄ or R₅ to form alkylene bridges between the terminal nitrogen and the alkyl portion of R₇ or R_{7a} groups to form 5 or 6 membered rings; or R₇ and R_{7a} can be joined to one another to form a C₃ cycloalkyl;

n is 2;

m is 0, 1, or 2;

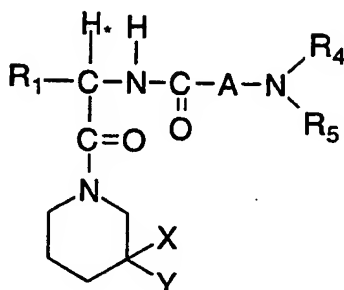
q is 0, 1, 2, or 3;

t is 0, 1, 2, or 3;

and pharmaceutically acceptable salts and individual diastereomers thereof.

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15. The compound of Claim 13 of the formula:



Formula C1b

wherein:

R₁ is selected from the group consisting of: C₁-C₁₀ alkyl, aryl (C₁-C₃ alkyl)-, (C₃-C₇ cycloalkyl)(C₁-C₃ alkyl)-, and aryl (C₀-C₁ alkyl)-K-(C₁-C₂ alkyl)-, where K is O or S(O)_m and the aryl is phenyl, pyridyl, naphthyl, indolyl, azaindolyl, or benzimidazolyl which is optionally substituted by 1-2 C₁-C₄ alkyl, 1 to 2 OR₂, S(O)_m R₂, or C(O)OR₂;

R₂ is hydrogen, C₁-C₆ alkyl, or C₃-C₇ cycloalkyl, and where two C₁-C₆ alkyl groups are present on one atom they may be optionally joined to form a C₅-C₇ cyclic ring optionally including oxygen, sulfur or NR_{3a}; R_{3a} is hydrogen, or C₁-C₄ alkyl;

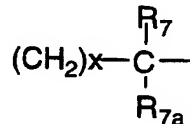
X is selected from: hydrogen, -(CH₂)_qN(R₂)C(O)R₂, -(CH₂)_qN(R₂)C(O)(CH₂)_taryl, -(CH₂)_qN(R₂)SO₂(CH₂)_taryl, -(CH₂)_qN(R₂)SO₂R₂, -(CH₂)_qN(R₂)C(O)N(R₂)(CH₂)_taryl, -(CH₂)_qN(R₂)C(O)N(R₂)(R₂), -(CH₂)_qC(O)N(R₂)(R₂), -(CH₂)_qN(R₂)C(O)OR₂, -(CH₂)_qC(O)N(R₂)(CH₂)_taryl, -(CH₂)_qC(O)OR₂, -(CH₂)_qC(O)O(CH₂)_taryl, -(CH₂)_qOC(O)R₂, -(CH₂)_qOC(O)(CH₂)_taryl, -(CH₂)_qS(O)_mR₂, and -(CH₂)_qS(O)_m(CH₂)_taryl, where an R₂ group may be optionally substituted by hydroxyl, carboxyl, -CONH₂, -S(O)_mCH₃, carboxylate C₁-C₄ alkyl esters or tetrazole and aryl is phenyl, naphthyl or pyridyl which may be further substituted by 1-2 halogen, 1 to 2 OR₂, C(O)OR₂, 1 to 3 C₁-C₄ alkyl, S(O)_mR₂, or 1H-tetrazole-5-yl;

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Y is selected from: hydrogen, C₁-C₈ alkyl, (CH₂)_taryl, -(CH₂)_q C₅-C₇ cycloalkyl, -(CH₂)_q-K-(C₁-C₆ alkyl), -(CH₂)_q-K-(CH₂)_taryl, and -(CH₂)_q-K-(CH₂)_t (C₅-C₆ cycloalkyl), where K is S(O)_m and where the alkyl groups may be optionally substituted by hydroxyl, carboxyl, CONH₂, carboxylate C₁-C₄ alkyl esters or 1H-tetrazole-5-yl and aryl is phenyl, naphthyl, pyridyl, thiazolyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl or imidazolyl which may be optionally substituted by 1 to 2 halogen, 1 to 2 OR₂, 1 to 2 -N(R₂)(R₂), CO(OR₂), 1 to 2 C₁-C₄ alkyl, S(O)_mR₂, or 1H-tetrazol-5-yl, with the proviso that if X is hydrogen, Y is other than hydrogen;

R₄ and R₅ are independently hydrogen, C₁-C₄ alkyl, or substituted C₁-C₃ alkyl where the substituents may be 1 to 2 hydroxyl;

A is



where x is 0, or 1;

R₇ and R_{7a} are independently hydrogen, C₁-C₆ alkyl, phenyl, substituted C₁-C₆ alkyl wherein the substituent is imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)_mR₂, or R₇ and R_{7a} may be joined to one another to form a C₃ cycloalkyl;

m is 0, 1, or 2;

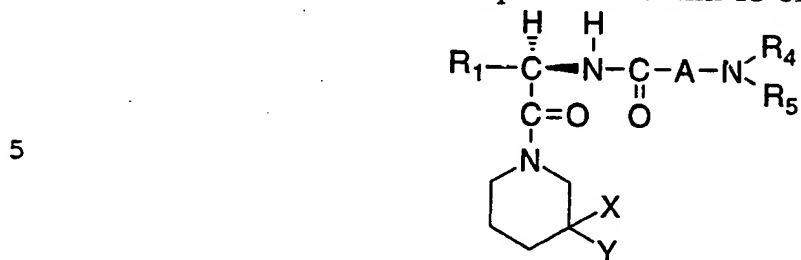
q is 0, 1, 2, or 3;

t is 0, 1, 2, or 3;

and pharmaceutically acceptable salts and individual diastereomers thereof.

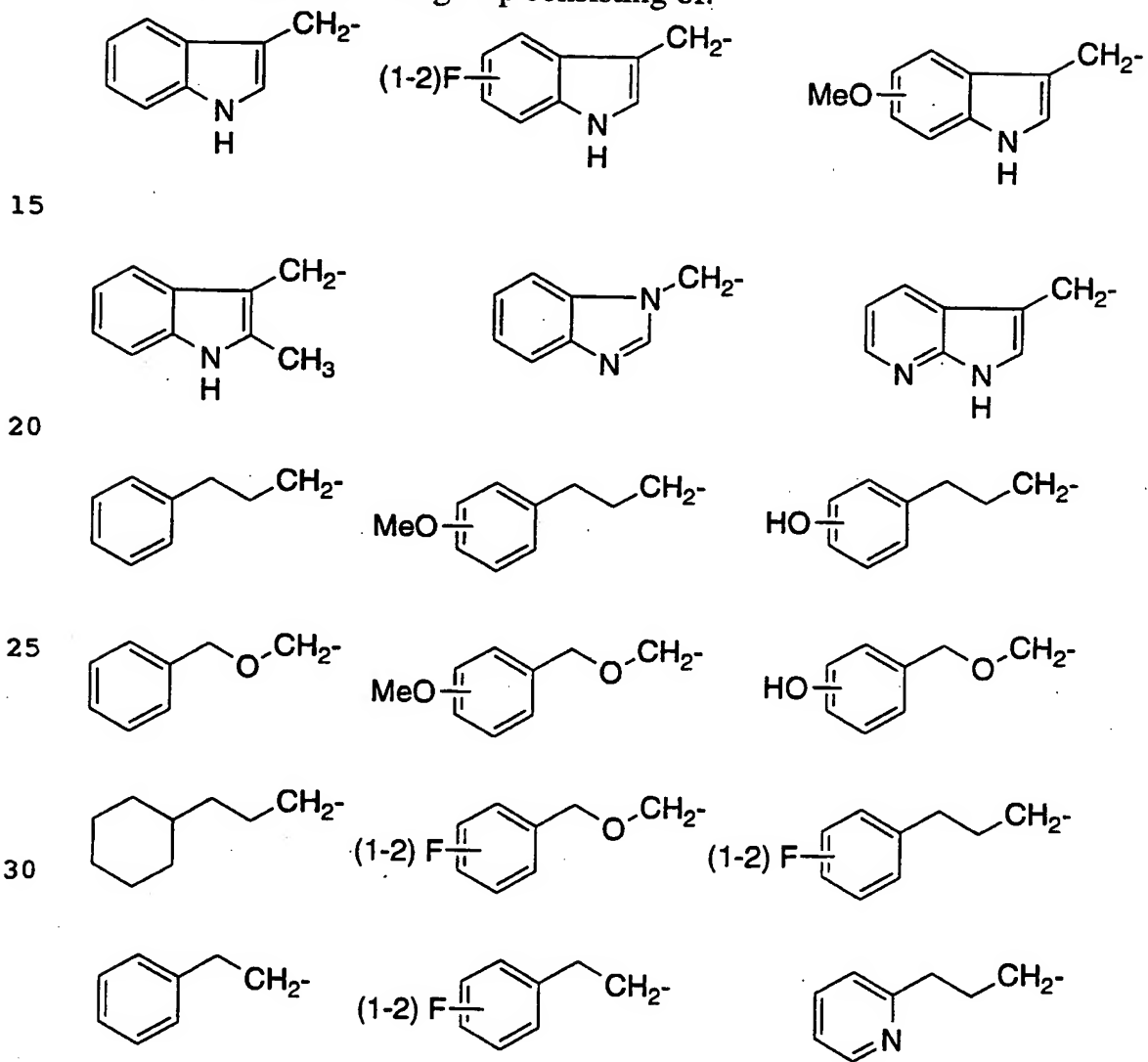
- 400 -

16. The compound of Claim 13 of the formula:



Formula CIc

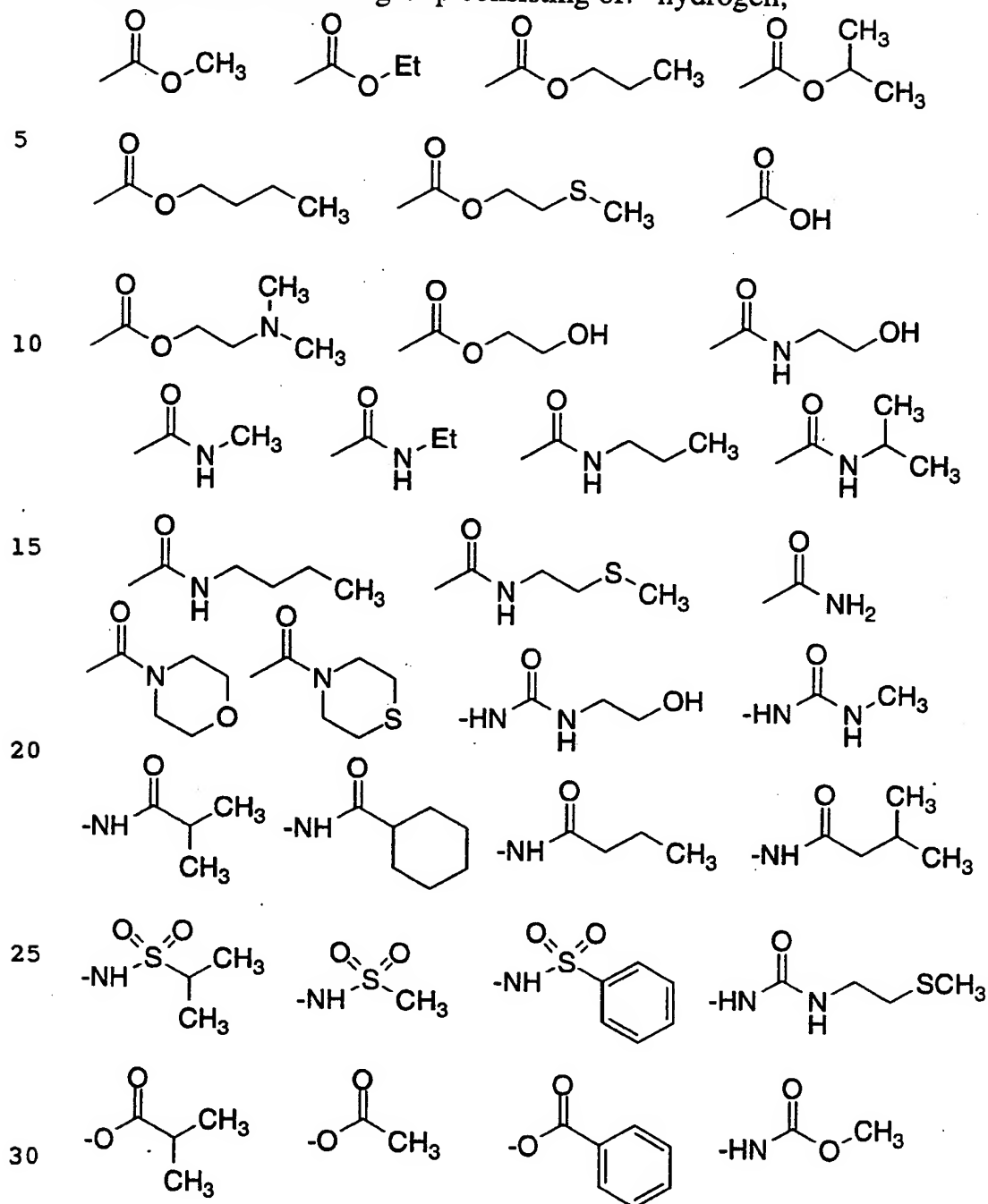
wherein:

10 R₁ is selected from the group consisting of:

or their regioisomers where not specified;

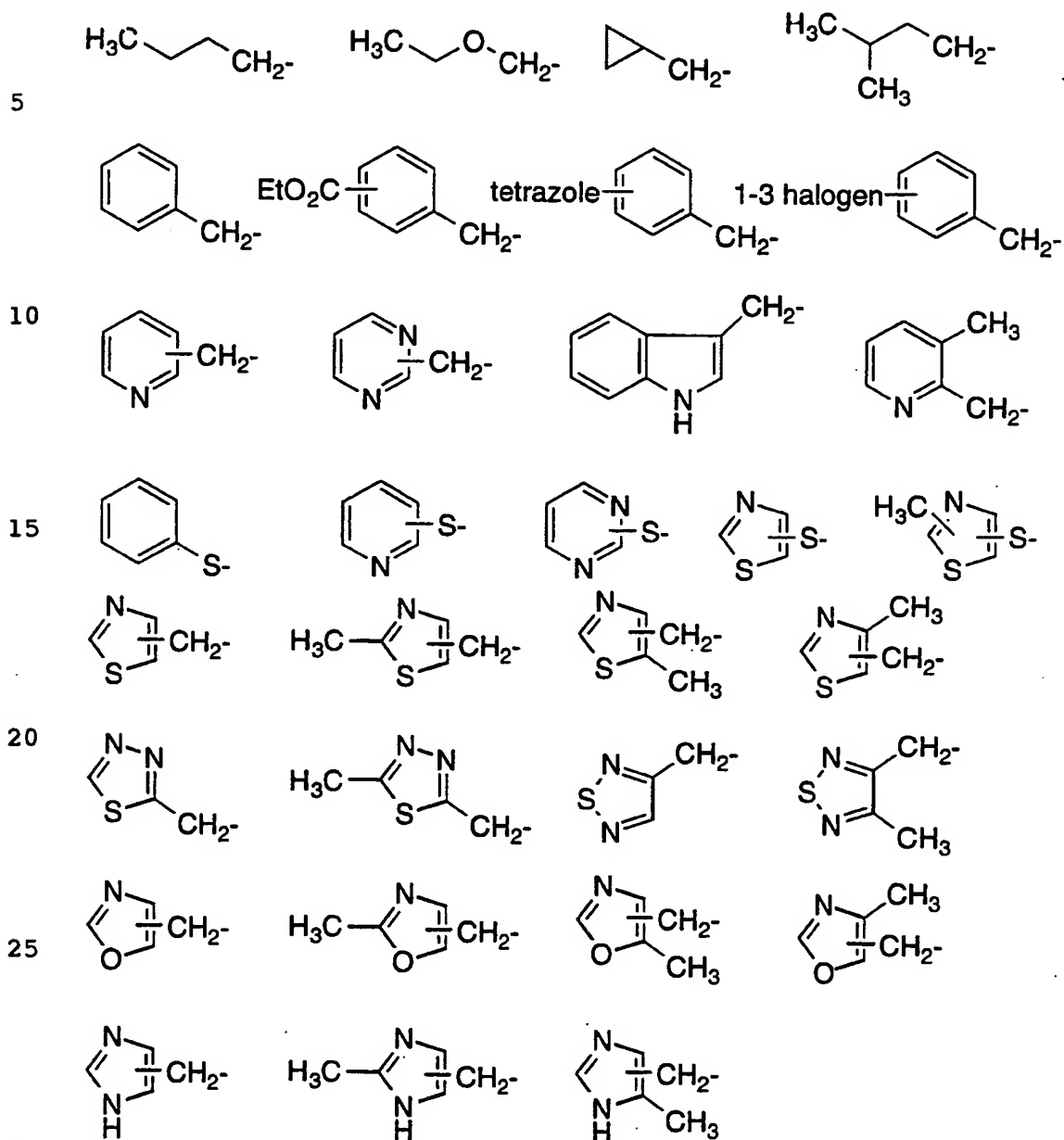
- 401 -

X is selected from the group consisting of: hydrogen,



- 402 -

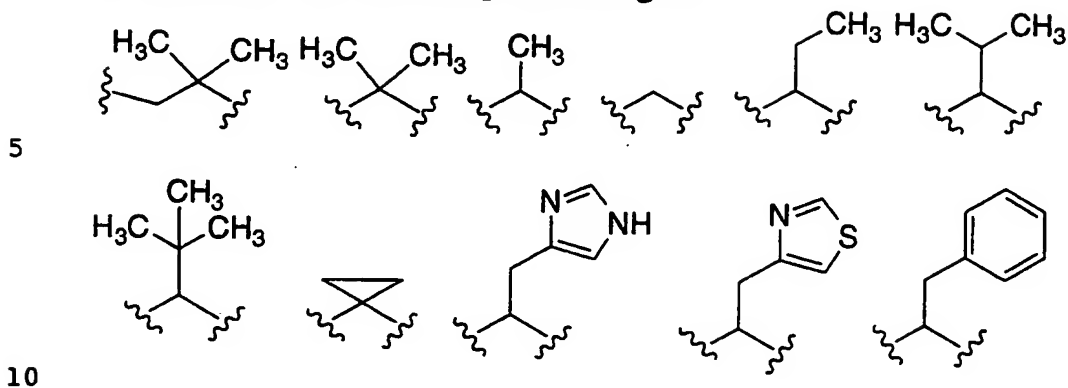
Y is selected from the group consisting of: hydrogen,



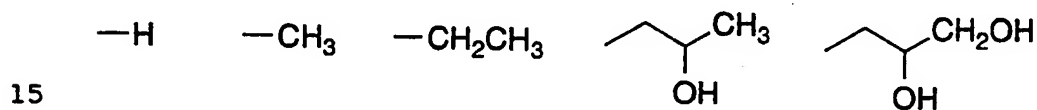
or their regioisomers whereof where not specified, with the proviso that if X is hydrogen, Y is other than hydrogen;

- 403 -

A is selected from the group consisting of:

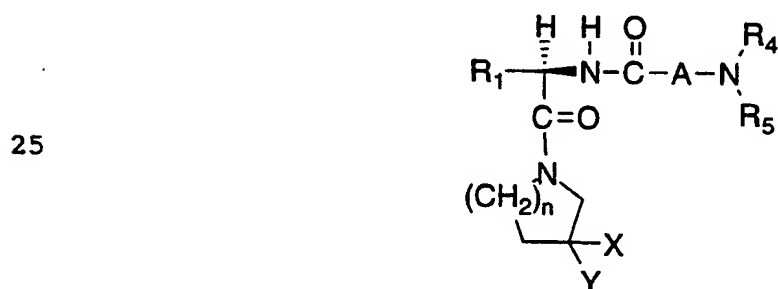


R4 and R5 are independently selected from the group consisting of:



and pharmaceutically acceptable salts and individual diastereomers thereof.

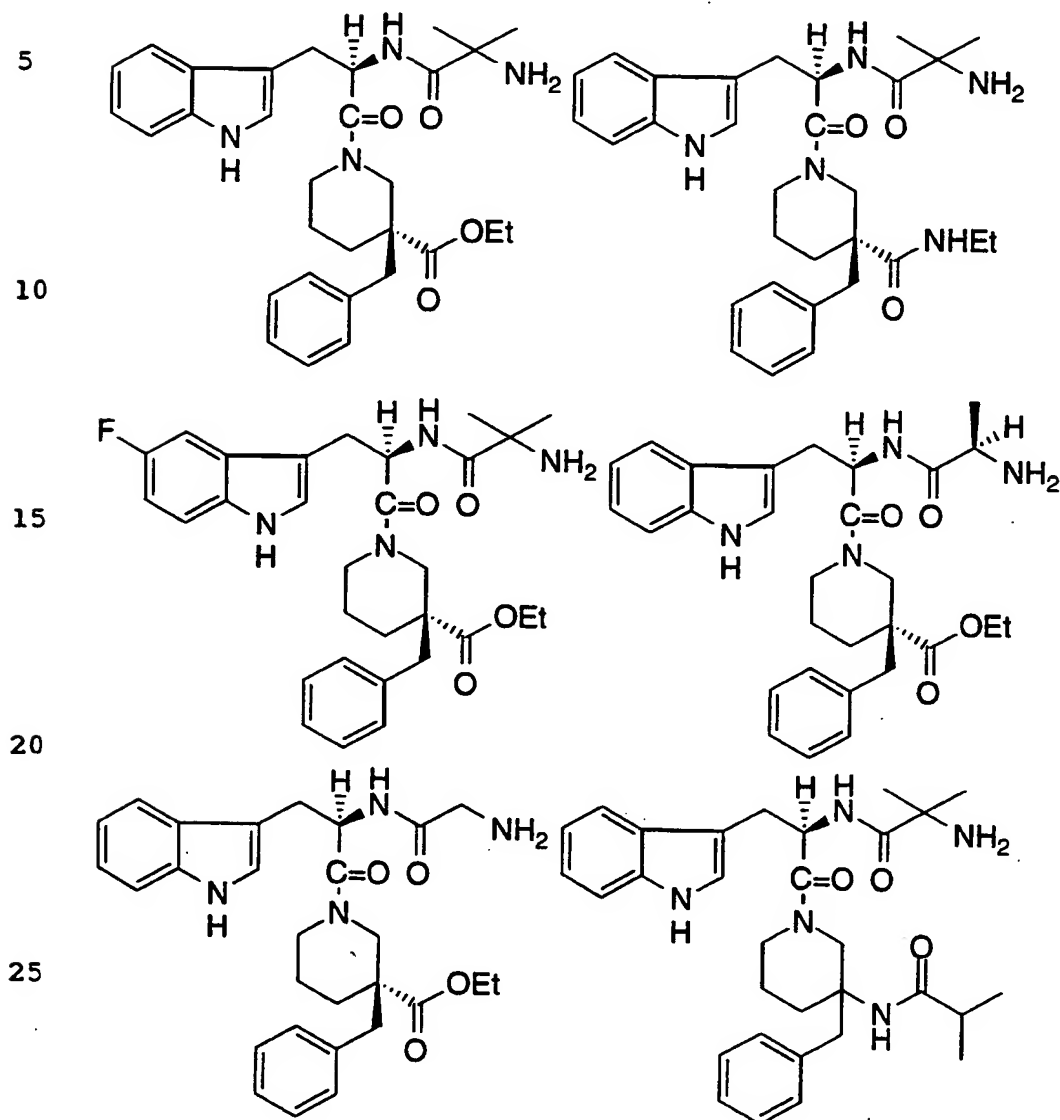
20 17. The stereospecifically defined compound of Claim 13 of the formula:



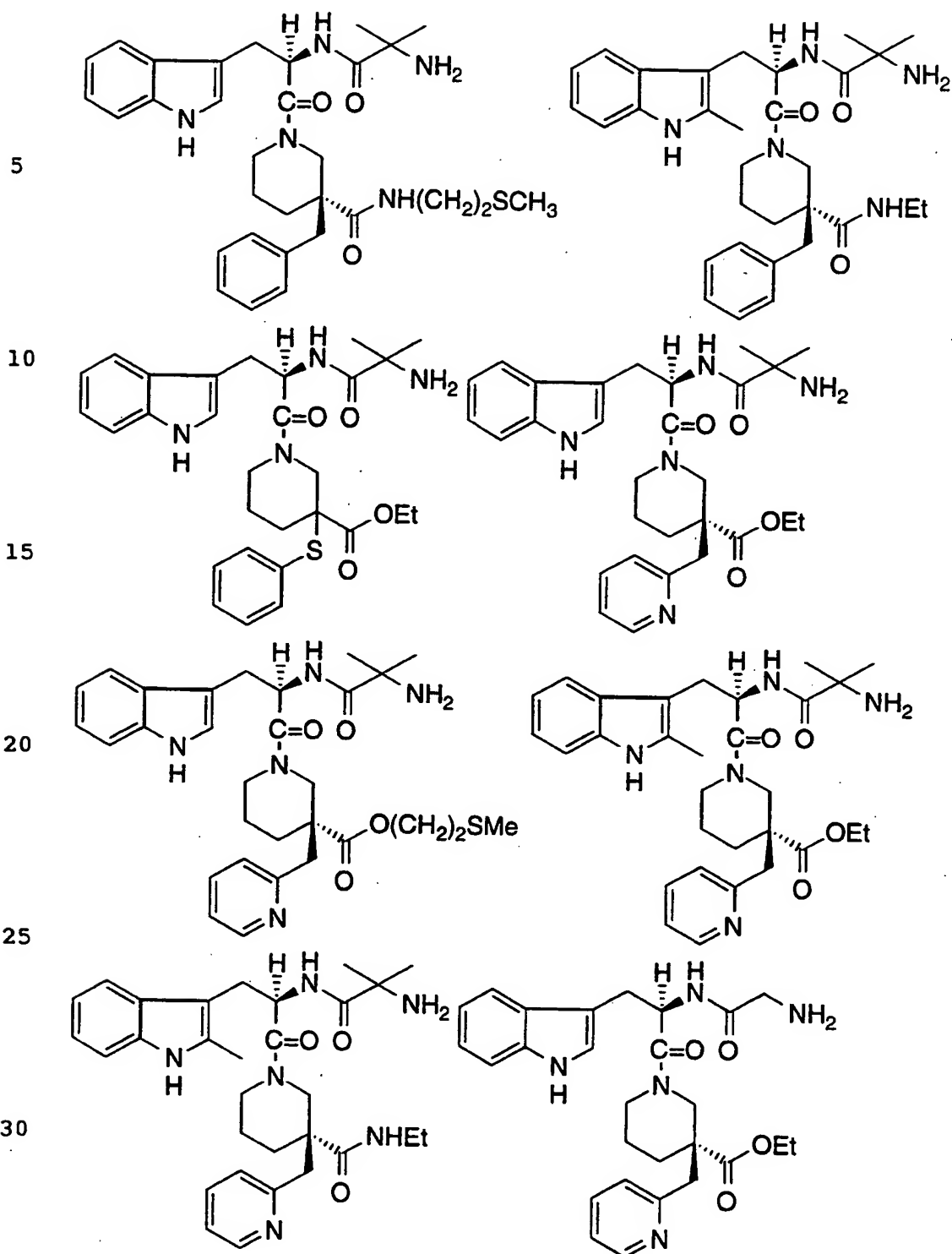
30 wherein R1, R4, R5, A, X, Y, and n are as defined in Claim 13.

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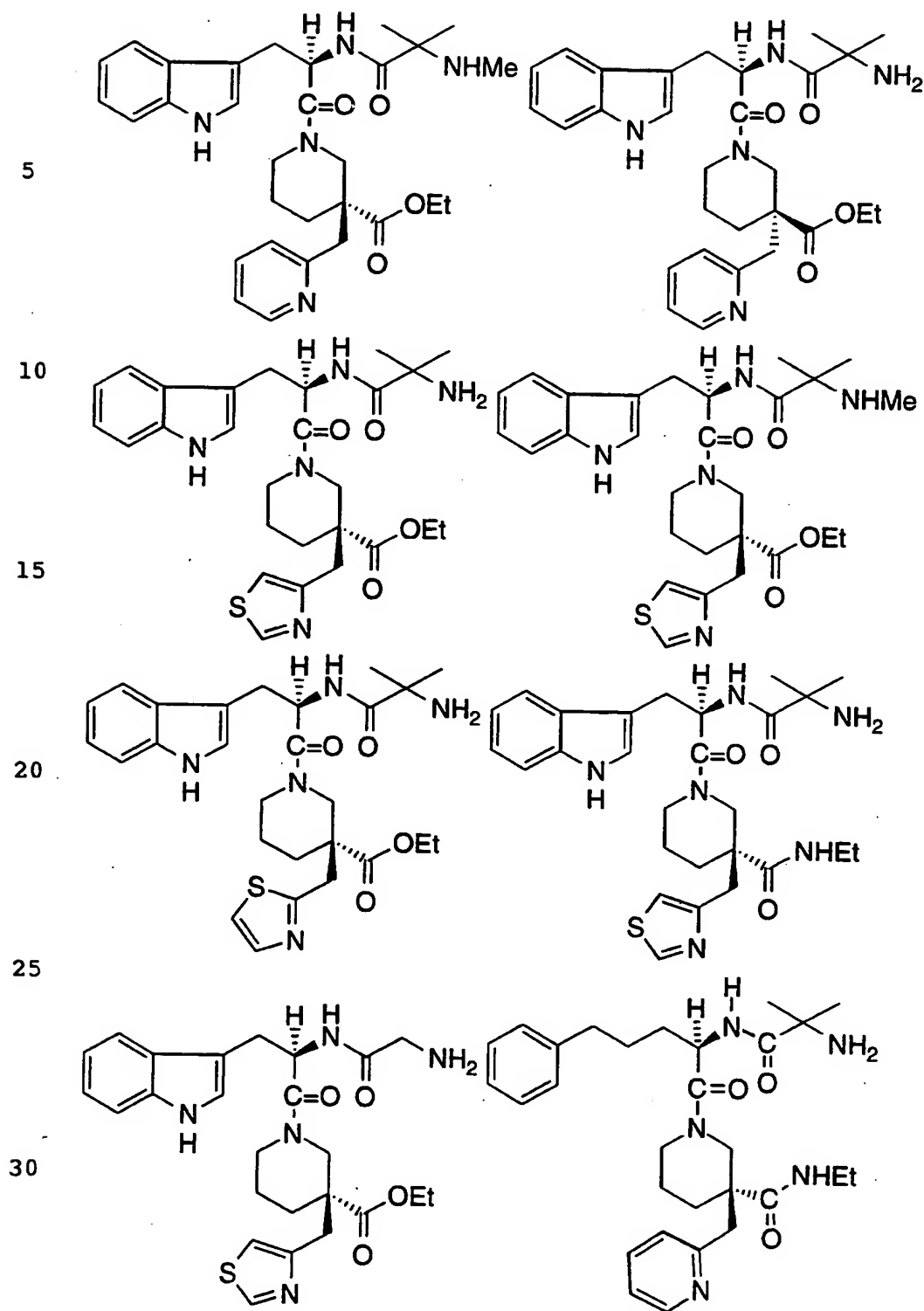
18. The compound of Claim 13 which is selected from the group consisting of:



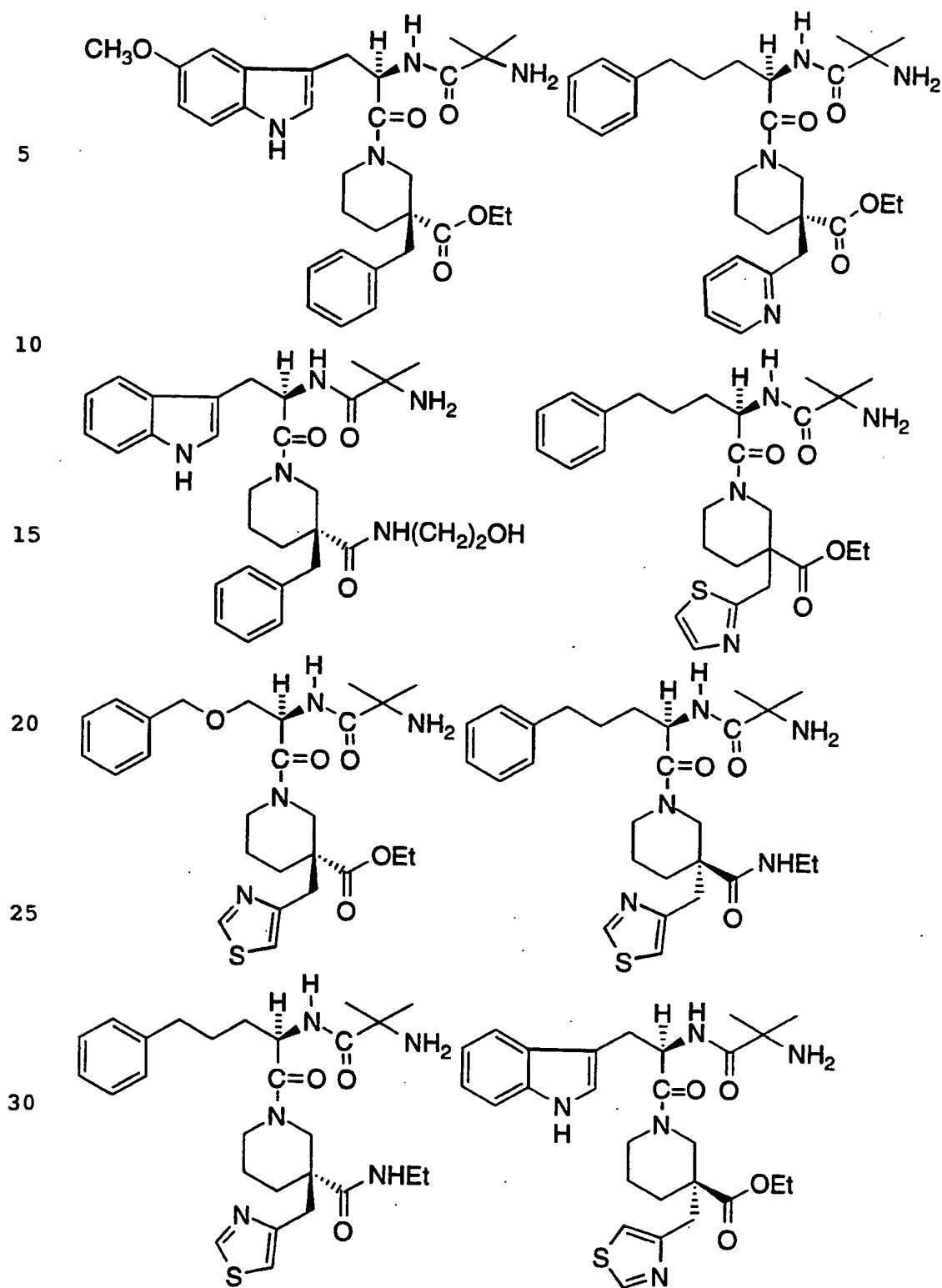
- 405 -



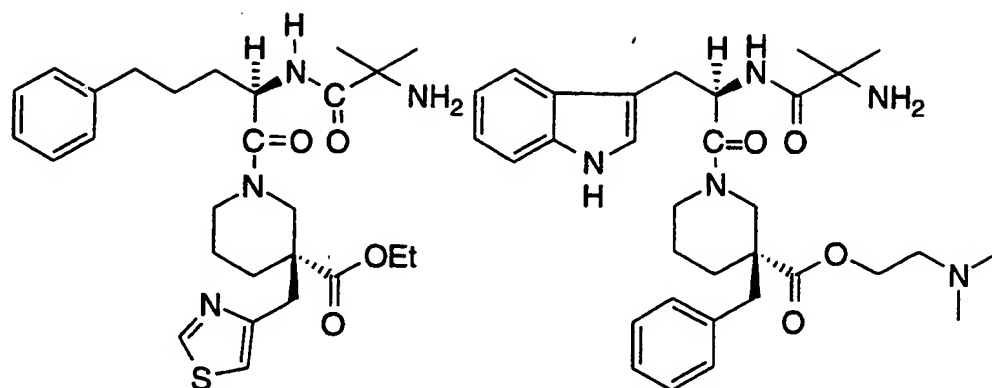
- 406 -



- 407 -



- 408 -



and their pharmaceutically acceptable salts and individual diastereomers thereof where not otherwise specified.

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19. A composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of a compound of Claim 1.

5

20. A composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier, an effective amount of a compound of Claim 1, and an additional growth hormone secretagogue.

10

21. The composition of Claim 20 wherein the additional growth hormone secretagogue is selected from the group consisting of: growth hormone releasing peptide GHRP-6; growth hormone releasing peptide GHRP-2; growth hormone releasing peptide GHRP-1; B-HT920; growth hormone releasing factor; an analog of growth hormone releasing factor; IGF-1 and IGF-2.

15

22. A composition useful for the treatment of osteoporosis which comprises a combination of a bisphosphonate compound and a compound of Claim 1.

20

23. The composition of Claim 22 wherein the bisphosphonate compound is alendronate.

25

24. A method for increasing levels of endogenous growth hormone in a human or an animal which comprises administering to such human or animal an effective amount of a compound of Claim 1.

30

25. A method for increasing feed efficiency, promoting growth, increasing milk production and improving the carcass quality of livestock which comprises administering to such livestock an effective amount of a compound of Claim 1.

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26. A method of treating or preventing a condition selected from the group consisting of: osteoporosis; catabolic illness; immune deficiency, including that in individuals with a depressed T4/T8 cell ratio; hip fracture; musculoskeletal impairment in the elderly; growth hormone deficiency in adults or in children; obesity; cachexia and protein loss due to chronic illness such as AIDS or cancer; and treating patients recovering from major surgery, wounds or burns, in a patient in need thereof which comprises the administration to the patient of an effective amount of the compound of Claim 1.

10

27. A method for the treatment of osteoporosis which comprises administering to a patient with osteoporosis a combination of a bisphosphonate compound and a compound of Claim 1.

15

28. The method of Claim 27 wherein the bisphosphonate compound is alendronate.

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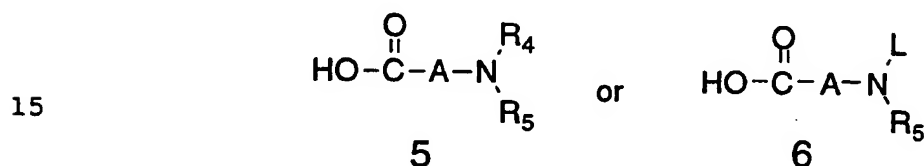
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- 411 -

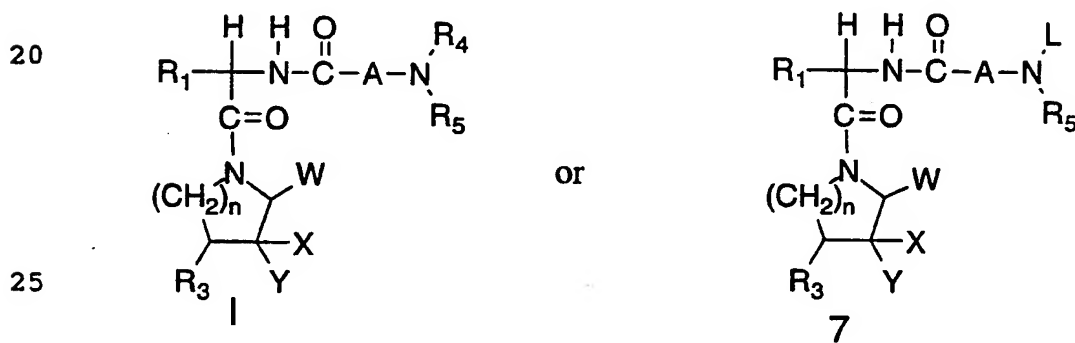
29. A process for the preparation of a compound of Claim 1 which comprises reacting a compound of the formula:



with a compound of the formula:



to give a compound of the formula:

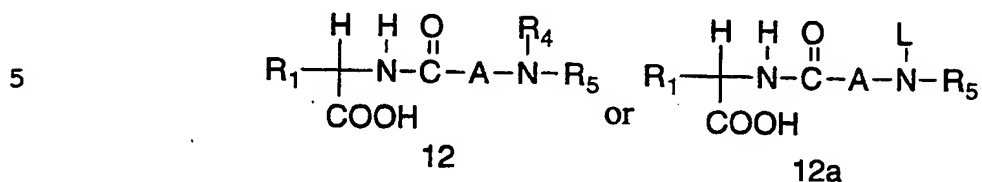


where R₁, R₃, R₄, R₅, A, W, X, Y and n are as defined in Claim 1 and L is a protecting group which is subsequently removed if present and salts are formed if desired.

30

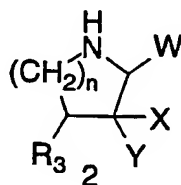
- 412 -

30. A process for the preparation of a compound of Claim 1 which comprises reacting a compound of the formula:

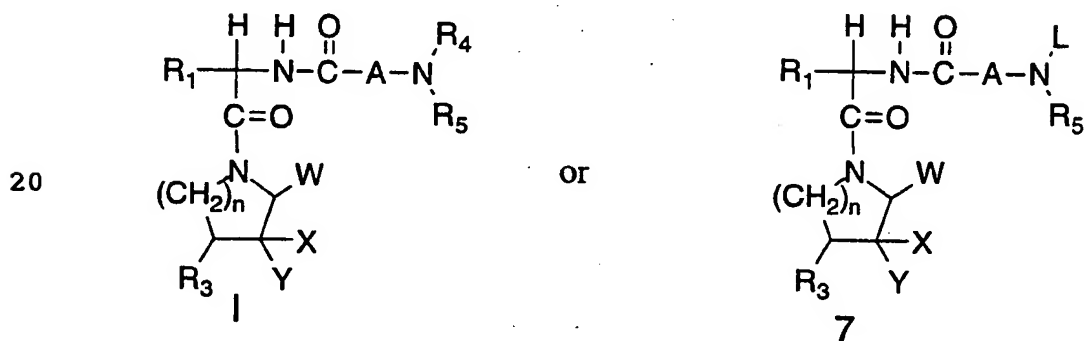


with a compound of the formula:

10



15 to give a compound of the formula:



25 where R₁, R₃, R₄, R₅, A, W, X, Y and n are as defined in Claim 1 and L is a protecting group which is subsequently removed if present and salts are formed if desired.

30

INTERNATIONAL SEARCH REPORT

International application N.
PCT/US94/12816

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/445; C07D 401/02, 401/14, 409/02

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) r to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, DIALOG MULTIDATABASE, BIOSIS, MEDLINE, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| A | US, A, 4,411,890 (MOMANY) 25 OCTOBER 1983, see entire document | 1-24, 26-28 |
| A | US, A, 4,782,139 (DIMARCHI ET AL) 01 NOVEMBER 1988, see entire document | 1-24, 26-28 |
| A | US, A, 5,084,442 (FELIX ET AL) 28 JANUARY 1992, see entire document | 1-24, 26-28 |
| A | US, A, 5,162,302 (COGBURN) 10 NOVEMBER 1992, see entire document | 1-24, 26-28 |
| Y | US, A, 4,299,821 (KISFALUDY ET AL) 10 NOVEMBER 1981, see column 22, line 24 | 1-5 |
| Y | US, A, 4,997,825, (WAGNER) 05 MARCH 1991, see column 2, lines 28-64 | 20-21 |

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | | | |
|--|--|----|---|
| Special categories of cited documents: | | T | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| *A | document defining the general state of the art which is not considered to be of particular relevance | | |
| *E | earlier document published on or after the international filing date | *X | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| *L | document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | *Y | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combinations being obvious to a person skilled in the art |
| *O | document referring to an oral disclosure, use, exhibition or other means | | |
| *P | document published prior to the international filing date but later than the priority date claimed | *A | document member of the same patent family |

Date of the actual completion of the international search

09 FEBRUARY 1995

Date of mailing of the international search report

030395

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/12816

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| Y | US, A, 5,036,045, (THORMER) 30 JULY 1991, COLUMN 3, LINES 15-53 | 20-21 |
| Y | US, A, 5,164,368 (RECKER) 17 NOVEMBER 1992, see column 4 lines 20-53 | 20-21 |
| Y | US, A, 5,276,014, (GLUCKMAN ET AL) 04 JANUARY 1994, see column 3, lines 30-35 | 20-21 |
| Y | US, A, 5,366,965, (STREIN) 22 NOVEMBER 1994, see entire document | 22, 23, 27, 28 |
| Y | US, A, 5,137,872, (SEELY ET AL) 11 AUGUST 1992, see columns 8-10 | 22, 23, 26-28 |
| Y | US, A, 5,284,841 (CHU ET AL) 08 FEBRUARY 1994, see column 48, line 28-column 49 line 5 | 26 |
| X Y | JP, A, 5-163,224 (MUKOYAMA ET AL) 29 JUNE 1993, see column 3 formula (c), column 11-12 compounds 7 and 8 | 13, 17 7-9 |
| X Y | CHEMICAL ABSTRACTS, Volume 113, No. 9 issued 27 August 1990, Sakamoto et al, "Chymotrypsin inhibition by dipeptide esters, phenylpiperidide and phenyl piperazides" see page 322, column 1, abstract no. 73560u, Pept, Chem. 1989, 27th, 375-8 | 7-9 13, 17 |
| X Y | CHEMICAL ABSTRACT, Volume 113, No. 15 issued 08 October 1990, Horwell et al. "alpha-methyl tryptophanyl phenyl alanines and their arylalanylamine "dipeptoid" analogs of the tetrapeptide cholecystokinin" see p. 715 column 2, abstract no. 132771p, Eur. J. Med. Chem. 25(1)53-60 | 13-15 7-11, 13-17 |

INTERNATIONAL SEARCH REPORT

I. national application No.
PCT/US94/12816

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-24, 26-28
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest



The additional search fees were accompanied by the applicant's protest.



No protest accompanied the payment of additional search fees.

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/256, 319, 322, 323, 324, 326, 362, 363, 365, 372, 394, 396, 414; 540/596, 597, 598, 601, 603, 607; 544/335; 546/193, 199, 201, 202, 205, 209, 210; 548/127, 128, 205, 214, 253, 306.1, 467, 468,

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/256, 319, 322, 323, 324, 326, 362, 363, 365, 372, 394, 396, 414,
540/596, 597, 598, 601, 603, 607,
544/335,
546/193, 199, 201, 202, 205, 209, 210,
548/127, 128, 205, 214, 253, 306.1, 467, 468,

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

I. Claims 1-19 and 24, compounds, compositions and method of increasing production or release of growth hormone in human;

II. Claims 20-21, composition for increasing growth hormone (GH) containing compounds and GH secretagogue;

III. Claims 22-23, 27-28, composition and method of using them in treating osteoporosis;

IV. Claim 25, method of increasing feed efficiency in live stock;

V. Claim 26, method of treating various diseases from cancer to AIDS;

VI. Claim 29, process 1 of making chemical compounds from choices of acids and amides;

VII. Claim 30, process 2 of making a chemical compounds from amino acids and cyclic imines.

This application contains inventions of groups I-VII which are not so linked to form a single inventive concept in compliance with PCT Rule 13.1-13.2. PCT 13.1 Rule states that the international application shall relate to one invention only or to a group of inventions so linked as to form "a single general inventive concept". PCT Rule 13.2 indicates that such unity of invention is fulfilled only when there is a "technical relationship" among those inventions involving one or more of the same or corresponding "special technical features". In the instant groups I-VII, a "technical relationship" corresponding to the "special technical features" is lacking because the special feature for groups I-VII are:

group I unique compounds, composition and method of using such depending on the structure and properties of the claimed compounds;

groups II-III, composition for treating diseases depending on the unique combination/active ingredients of each claimed composition;

group IV-V method of treating distinct diseases depending on the steps, locations, dosage, sequence etc. of administration of a drug or drug combination;

groups VI-VII processes depending on the starting material, sequence, and conditions of the chemical reactions.

Therefore, no linkage which forms a single general inventive concept can be established among the different inventions.